Medical
Hist

SURGERY, GYNECOLOGY AND OBSTETRICS

AN INTERNATIONAL MAGAZINE, PUBLISHED MONTHLY

VOLUME 62 JANUARY, 1936 NUMBER 1

A REVIEW CLINICAL AND PATHOLOGICAL OF PARAHYPOPHYSEAL LESIONS[1]

CHARLES H. FRAZIER, M.D., Sc.D., F.A.C.S., PHILADELPHIA, PENNSYLVANIA

ONE has but to glance at the pages of the medical history of this country to realize that the name of Philadelphia is closely knit to medical tradition—the home of the first medical school, of the first hospital as its clinical laboratory, of the first public health endowment to promote public health as a profession, of the first hospital clinic for teaching, and of many other pioneer institutions. The chapter of surgery would be far from complete without the name of William Shippen, Jr., the special pupil of William Hunter; of Philip Syng Physick, called the father of American surgery; of William Gibson; of John Rhea Barton; of George McClellan; and George W. Norris, ranked among the best surgical writers of his day; of Thomas Muetter; of Joseph Pancoast; of D. Hayes Agnew; of Samuel D. Gross; of W. W. Keen.

Thomas Muetter, born in Virginia in 1811, graduate of the University of Pennsylvania; professor of surgery, Jefferson Medical College, celebrated for his plastic operations for extensive scars, died in 1859. May 1 of this year, the College of Physicians agreed to change its location to Thirteenth and Locust Streets and his widow offered to deposit his library and pathological museum with the College when a permanent building for its reception should be constructed. Through this benefaction the Muetter Museum and the Muetter Lectureship were established.

Since the inauguration of this foundation many deposits have been made in the Museum and 46 lectures have been delivered.

In London on November 27 of the present year,[1] exercises were held to commemorate the Jubilee of the first operation for the removal of a tumor from the brain performed by Sir John Rickman Godlee, but we are inclined to associate the name of Sir Victor Horsley with the recognition of neurosurgery as a special field of surgical endeavor. Since that time and more particularly since the beginning of this century, neurosurgery has been recognized as a special calling, and for this credit must be ascribed to the United States. Not for a long while, in fact not until recent years, did the countries across the Atlantic begin to train personnel for this specialty.

The extraordinary advances in the surgery of brain tumors is a matter of common knowledge. In 1894 at a meeting of the American Neurological Association, one of its members reported a series of 3 cases of brain tumors treated by massive doses of potassium iodide and of this number 2 were alleged to be markedly improved. What a transition from 1894 to 1934!

One could not begin to encompass now in a single treatise the problems of the surgery of brain tumor, so diversified and so differentiated have they become, no more than one could, in one treatise the surgery of abdominal

[1] Muetter Lecture delivered under the auspices of the College of Physicians of Philadelphia, December 6, 1934.

tumors. Since the notable contribution of Cajal to the differentiation of glial cells, one could not in a reasonable time comprehend the many questions that concern even a single type of tumor—the glioma.

In search for a subject appropriate for this Muetter Lecture, the author has chosen to consider the problems of brain tumors from a regional viewpoint and will present a collective review of the lesions that may be styled parasellar. Within the limitations of a space no greater in diameter than half a dollar, one may find at operation any one of eight lesions, —lesions that differ from one another in their source of origin, in their histological components, in their clinical behavior, in their influence upon the expectation of life, in their management on the operating table, to wit:

I. Intracranial aneurisms.
II. Tumors of the optic chiasm.
III. Sphenoidal ridge tumors.
IV. Pseudotumors.
V. Rathke's cleft tumors.
VI. Hypophyseal stalk tumors.
VII. Suprasellar fibroblastomas.
VIII. Suprasellar adenomas.

GROUP I. PARASELLAR ANEURISMS

When considering lesions in the parasellar area, one must bear in mind the possibility of aneurisms of the circle of Willis. Those which arise from the internal carotid artery, from the middle cerebral and the posterior communicating vessels, may properly be considered as in this territory. As to the incidence of intracranial aneurisms: Osler found 12 in 800 autopsies and Pitt 23 in 900 autopsies. Of 154 assembled by Gowers, 23 arose from the internal carotid artery, 44 from the middle cerebral, and 8 from the posterior communicating artery. Approximately half of the total number originated in the territory with which at present we are concerned.

The cause of cerebral aneurisms is not clear. Syphilis plays a very unimportant part even in young individuals. A congenital weakness of the vessels at the point of bifurcation with a defect in the muscularis has been advocated warmly and appears to have some basis in fact. In older individuals, unquestionably arteriosclerosis is a factor. Mycotic aneurisms when they occur are more common in the cerebral than in the basilar vessels. In the case I am about to cite the patient was in her twentieth year with no definite sclerosis of the vessels, and it seems reasonable to assume that the aneurism was of congenital origin, that is, due to a congenital defect in the muscularis.

CASE 1. A month ago for a period of a week a young woman had attacks of nausea, vomiting, and headache with pain referred behind and over the right eye. A second attack followed with paralysis of the third and fourth cranial nerves. While under observation she became comatose, developed a right hemiparesis, and died. The autopsy revealed a ruptured aneurism of the posterior communicating artery, probably congenital in origin.

Clinical history. H. M. K., aged 20 years, (File No. 19645), was admitted to the Neurosurgical Service of the University Hospital August 8, 1930. Briefly, the history was as follows:

June 29, 1930, the patient stepped into a swimming pool and suddenly developed a right sided headache. Pain was referred chiefly over and behind the right eye. She became nauseated and vomited but did not lose consciousness. The nausea persisted for 2 days and the headache for 5 days. She remained in bed 1 week and returned to her occupation as a professional nurse in 3 weeks.

August 1, 1930, a month after the initial attack, she felt faint and vomited several times. Headache was present but less severe than aforetime. August 2 she developed an oculomotor palsy. Her menstrual periods had been irregular for 4 months.

August 21, 1930, with the exception of paralysis of the third and fourth cranial nerves there were no neurological signs except a slight cut in the left temporal field (Fig. 1). The serological reactions were negative and there was no blood in the cerebrospinal fluid.

August 22, 1930, she was found unconscious in the bathroom. She remained comatose or semicomatose, developed a right hemiparesis, and died August 27.

Autopsy revealed a ruptured aneurism of the posterior communicating artery, with hemorrhage into the right ventricle, a subarachnoid hemorrhage at the base and covering the entire right cerebral hemisphere. The brain was markedly edematous. The origin of the aneurism was obscure unless it was congenital. According to Dr. B. J. Alpers, there were changes in the carotid vessels which strongly suggested the chronic vascular syphilis of Jacob. (Fig. 2.)

Upon reviewing this history one is impressed with certain features characteristic of aneurism and chiefly with the periods of active symptoms and remissions, associated with a sudden and otherwise unaccountable paralysis of the oculomotor nerve. In this case the

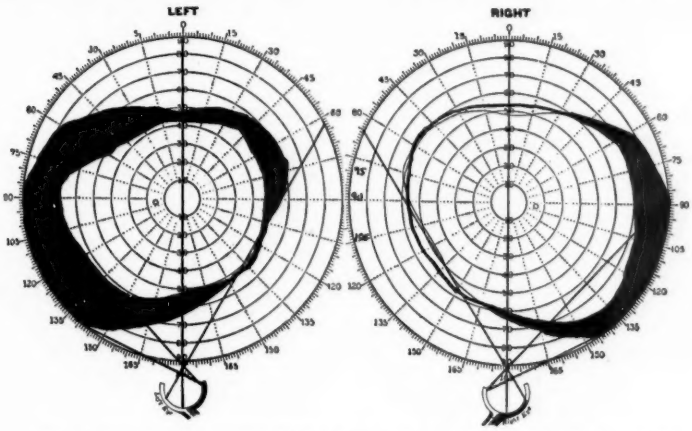


Fig. 1. Case 1. Contraction field of left eye in an intracranial aneurism of the posterior communicating artery.

interval of freedom was comparatively short, though in others months and years may elapse between the attacks.

In addition to the oculomotor paralysis, the fourth cranial nerve and the ophthalmic division of the fifth were involved. Furthermore the patient had had the intense headache that so frequently accompanies leakage. It is not without reason to assume that the irregular menses were due to pressure on the hypophysis. Among the ocular phenomena of parasellar aneurisms may be included field defects

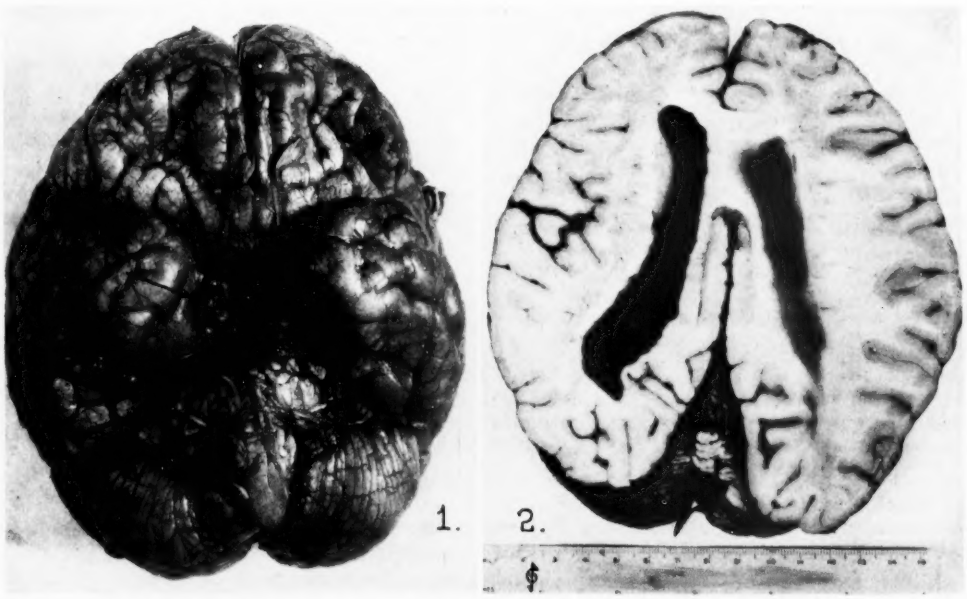


Fig. 2. Case 1. Left, The arrow indicates a small aneurism arising from posterior communicating artery and compressing the oculomotor nerve. Right, Section of brain showing intraventricular hemorrhage which caused death.

Fig. 3. Case 2. A large saccular aneurism, *A*, on the left arising from the internal carotid and a smaller one, *B*, on the right arising from the same vessel.

(as in this case), ptosis, strabismus, diplopia, proptosis, edema of the eyelids, and venous engorgement from pressure on the cavernous sinus.

The second case to which I will refer differs from the first in that there was definite evidence of arteriosclerosis of the circle of Willis and the patient was in his fifty-third year. But there was in this case no oculomotor or other ocular palsy. The outstanding symptom was an intense paroxysmal pain in the ophthalmic division of the trigeminus.

CASE 2. A middle aged man, 5 months before admission to the hospital in the course of 3 weeks, had a series of attacks characterized by intense headache, left frontal neuralgia, and momentary unconsciousness. Then followed a remission until 3 weeks before admission when he suffered intense paroxysmal pain in the distribution of the ophthalmic division of the trigeminus. Under the assumption that he had trigeminal neuralgia he came to the University Hospital and died without any forewarning 4 hours after admission. Diagnosis: large aneurism of the left, and a small aneurism of the right internal carotid artery.

Clinical history. R. W. M., aged 53 years (File No. 24987), was admitted to the Neurosurgical Service of the University Hospital August 12, 1932. Except for a latent tuberculosis, the patient was well until March 3 when he felt nauseated on arising and lost consciousness for a few moments. These attacks of nausea and unconsciousness recurred several times a day for a week and were accompanied by an intense bifrontal headache and extreme tenderness of the left side of the forehead. He complained at times of smelling a foul odor. Meanwhile there were no visual disturbances. Three weeks after the onset of these attacks the symptoms subsided, but 3 weeks ago he began to complain of shooting pains over the left eye, more or less paroxysmal. The patient, a physician, thought he had trigeminal neuralgia and decided to consult Dr. Frazier. His wife stated that he had become somewhat disorientated, had a poor memory for recent events, was emotionally unstable and increasingly irritable. He was admitted to the Hospital at 6:45 p.m. and died suddenly 4 hours later.

Examination. At the preliminary examination it was noted that the pupils were small, equal, and reacted promptly to light and accommodation. There were no ocular palsies and the fields were grossly normal. The right tendon reflexes were hyperactive, with an unsustained ankle clonus. In other respects the examination was negative.

Autopsy. At the autopsy there was revealed a thick subarachnoid hemorrhage which extended from the basilar area to the lower end of the medulla. An aneurism 2.5 by 3 centimeters in diameter was found in the left internal carotid artery, just below its junction with the middle and inferior cerebral arteries. The aneurism compressed the diencephalon and mesencephalon and extended laterally into the uncus and hippocampal gyrus of the left temporal lobe. The left oculomotor and left optic nerves appeared compressed. There was a small aneurism at the junction of the right internal carotid and middle cerebral artery. There was definite arteriosclerosis of the circle of Willis (Fig. 3).

In this as in the preceding case, despite the fact that there were no ocular palsies, there was the history of attacks, which suggested leakage, followed by remissions. In the case under consideration, the attacks were characterized by intense headache and periods of momentary unconsciousness. Intense headache, rigidity of the neck, ocular palsies, and a positive Kernig sign of sudden onset, if not immediately fatal, should always arouse one's suspicion of intracranial aneurism.

Were one to consider differentiation from a parasellar tumor, the gradual onset of the symptoms in tumors should at once eliminate the likelihood of an aneurism. To be sure, a parasellar tumor may cause pressure on the third, fourth, and fifth cranial nerves, often with field defects, but the patient never ex-

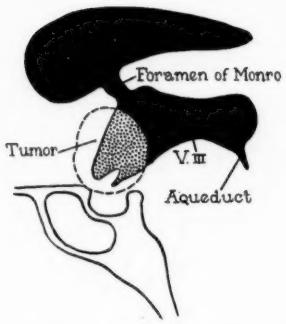


Fig. 4. The deformity produced by gliomas of the optic chiasm as shown by lipiodol injection into the ventricles. The anterior portion of the third ventricle and the infundibulum (dotted area) are obliterated by tumor. The sella is normal.

Fig. 5. Case 3. Glioma of right optic nerve.

hibits the signs of leakage or rupture, the intense headache and the stiff neck, with blood in the cerebrospinal fluid. Nor in the history of the tumor case are there striking periods of remission.

GROUP II. TUMORS OF THE OPTIC NERVES AND CHIASM

Although relatively infrequent, mention must be made in this review of tumors of the optic nerves and chiasm. In the past, in most instances, the precise diagnosis was not established until the lesion was exposed on the operating table. However, in some instances the clue has been suggested if the roentgenogram reveals enlarged optic foramina and expansion forward of the anterior wall of the sella turcica, and more recently, Balado and Pardal by means of injection of iodized oil into the lateral ventricles have found that there is a characteristic appearance of the ventricular system in glioma of the optic chiasm. There is a disappearance of that part of the third ventricle corresponding to the infundibulum and optic recess. The sella turcica is normal (Fig. 4).

The structure of the chiasmal gliomas seems to vary a great deal. Verhoeff believes that all tumors of the optic nerve and chiasm are gliomas, though many have been reported as neuromas, myxomas, fibromas, and tumors of other types. Verhoeff divides the gliomas into (1) a finely reticulated type, (2) a coarsely reticulated type, and (3) a spindle cell or coarsely fibrillated type.

That the structures of these gliomas may vary is shown by the fact that gliomas resembling oligodendroglioma and glioblastoma multiforme have been reported. Hortega finds some of these tumors have a myxomatous or fibrous appearance. He believes that the gliomas of the optic nerve are polymorphous in type.

Without these specific X-ray findings, the diagnosis of glioma of the optic nerves and chiasm is speculative. These tumors may involve but one or both optic nerves and the chiasms as well and appear as bulbous enlargements. While at first the lesion is confined within the sheath of the nerve or nerves, eventually it may expand and reach beyond these limitations.

When the tumor is of small dimensions, the clinical expression may be represented only by optic atrophy, field defects, and loss of visual acuity. One should remember the possibility of hysteria when there are signs only of visual defects and visual loss. Such was the case in a patient, a young woman, who had marked concentric contraction of the visual fields and an apparent loss in vision. She had been told elsewhere that she had a tumor of the optic chiasm with no hope of relief. The hysterical origin of the lesion was suspected and under a single galvanic shock the fields immediately expanded to normal and vision was restored to normal. As time goes on and the tumor grows headache may develop, there may be signs of hypophyseal dysfunction with the characteristic alterations in the sella and optic foramina.

As in the case about to be recorded, these tumors appear most frequently in children. The inevitable blindness that would follow a radical removal has placed these lesions in the inoperable class.

CASE 3. A boy, 12 years old, had complained of defective vision and headache. He was short of stature but with no outstanding signs of hypophyseal dysfunction. Except for a bitemporal hemianopsia and a bilateral optic atrophy, the findings were essentially negative. Operation revealed a tumor of the right optic nerve (Fig. 5).

Clinical history. W. G., aged 12 years (File No. 88816 G. H.), was referred to Dr. F. C. Grant on November 10, 1930, with the chief complaint of dimness of vision. September, 1930, the child was referred to Wills Eye Hospital because of a visual defect. He had difficulty in reading and held the print to the left side of the face. He had complained of headache for 3 months, was listless and tired easily.

Examination. With the exception of the visual disturbances, nothing was observed in the neurological examination except hyperactive abdominal reflexes, a hyperactive left patellar reflex, and a bilateral Babinski. The X-ray of the head and pituitary fossa and the serological tests were negative.

Ophthalmic report. There was no disturbance of ocular motility. Pupillary reflexes were normal, the left pupil slightly smaller. The consensual reflex was present and convergence was good. With ophthalmic light the field of vision in the right eye was lost except in the inferior nasal quadrant. In the left eye the vision was maintained in both the inferior and superior quadrants. There was a bilateral optic atrophy.

Operation. November 22, 1930. Right transfrontal craniotomy. Upon elevation of the right frontal lobe a small tumor was exposed, about 1 centimeter in diameter, taking its origin from and involving the right optic nerve. It seemed to rest upon the anterior clinoid process. Upon further exploration the tumor seemed to involve the left optic nerve as well. Two nubbins of tumor were removed from the right optic nerve and after this procedure the wound was closed.

Pathological diagnosis. Glioma.

GROUP III. TUMORS OF THE LESSER WING OF THE SPHENOID

The most common location for parasellar tumors is the sphenoidal ridge, a term given to that portion of the sphenoid bone formed by the lesser and greater wings. Tumors involving the sphenoidal ridge may be located either on the lesser or greater wings, but since only those located on the lesser wing may be looked upon as true parasellar tumors only those will be considered.

Histologically the most common tumor in this area, far outnumbering all others, is the meningeal fibroblastoma. At times gliomas involving the mesial aspect of the temporal lobe may spread over the adjacent sphenoid wings of the sphenoid bone, but these are not primary tumors of this region. Rarely, an hypophyseal adenoma may expand laterally and involve the lesser sphenoidal wing, but by and large, the great majority, if not all of the primary tumors arising along the lesser sphenoidal ridge are meningeal fibroblastomas. These tumors are encapsulated but may be so firmly attached to the dura overlying the ridge that they cannot readily be removed *in toto*. They vary in size (Figs. 6 and 7) from tumors only 1.5 to 2 centimeters in diameter and confined entirely to the ridge, to others which are 4 to 5 centimeters in diameter, extend forward into the anterior fossa or even backward into the adjacent middle fossa. Tumors confined to the lesser wing of the sphenoid bone are rare and give rise to few symptoms; when present, however, the latter are quite characteristic, and if the tumor be promptly recognized it may readily be removed. However, when the tumor has expanded into the anterior and middle fossa, the surgical problem becomes more difficult (Fig. 8). In the anterior fossa these tumors usually grow along the olfactory groove, hollowing out a place under the frontal lobe; in the middle fossa they make their beds under the temporal lobe. Sometimes the tumors are indented by a deep fissure where they have straddled the ridge.

Their histological structure is quite uniform. They present for the most part typical features of the meningeal fibroblastoma, with a well defined capsule, streams and whorls of cells, with varying amounts of collagen and fibroglia. Not all are of this type, however, for I have in my series two specimens that are classified as hemangio-endotheliomas.

Why is it that the suprasellar fibroblastomas, those arising from the tuberculum sellæ and the parasellar fibroblastomas springing from the lesser sphenoid ridge occur more frequently than the fibroblastomas arising at any

Fig. 6. Small sphenoidal ridge tumor.

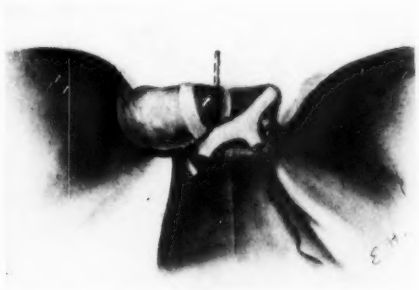


Fig. 7. Medium sized sphenoidal ridge tumor with the left optic nerve overstretched.

other point on the base of the skull? As demonstrated by Schmidt and others, these tumors arise from the arachnoidal villi the histological structure of which they resemble closely. Since the number of these villi is greater in the region of the sella turcica than at other points on the base of the skull, it is not surprising that these tumors occur in greater numbers in what appear to be these sites of predilection (Fig. 9).

Sphenoidal ridge tumors of the lesser wing are lateral to the sella turcica, on one side or the other, and by virtue of their location may produce changes in the bony structure detectable by X-ray. There may be an unilateral erosion of the sella turcica, an erosion of the dorsum sellæ, and posterior clinoid processes with destruction of the sellar floor on one side or destruction of the wing itself. In some cases there may be an enlargement of the optic foramen on the side of the tumor. More often there is destruction of the adjacent posterior clinoids and erosion of the dorsum sellæ. Before discussing the clinical manifestations, we submit by way of illustration the following case:

CASE 4. A small tumor of the left sphenoid ridge arising from the lesser wing. Progressive symptoms for 1 year. Bilateral primary optic atrophy. Visual acuity, 20/200 in both eyes. Right homonymous hemianopsia. Slight right facial weakness. Impairment of taste. Weakness of the right hand. Basal metabolic rate, minus 12. Normal intracranial pressure. Sella turcica "top normal" in size, 12 by 6 millimeters.

Clinical history. J. F., a man, aged 37 years (File No. 20020), 1 year before entrance had noticed impairment of vision. Vision continued to fail, but he

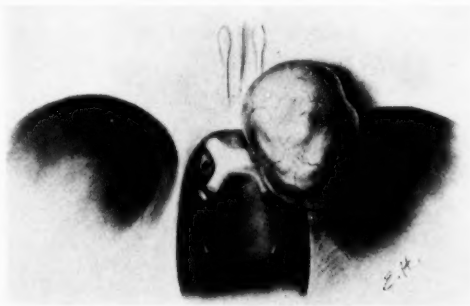


Fig. 8. Large sphenoidal ridge tumor encroaching on optic chiasm, spreading into anterior and middle fossæ.

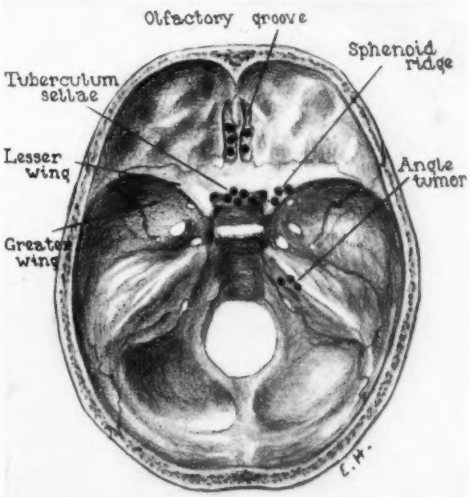


Fig. 9. Base of the skull showing the favorite sites of the basilar fibroblastomas.

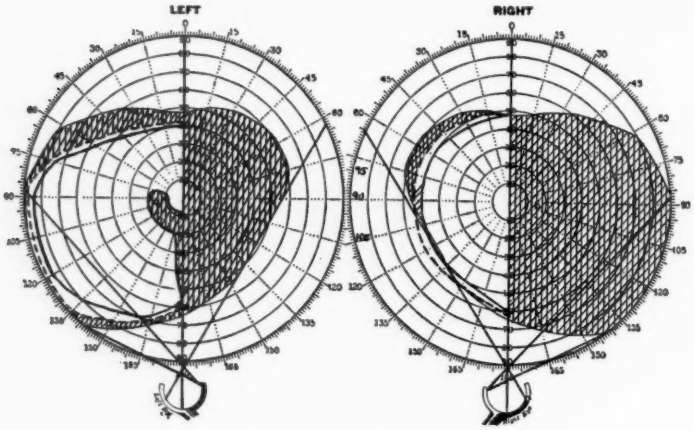


Fig. 10. Case 4. Fields before operation (October 7, 1930). Vision—left eye, 20/200; right eye, 20/200. Homonymous hemianopsia extending through the fixation point.

was able to work until 2 weeks before entrance to the hospital. Coincident with the visual disturbances he had fleeting pains in the head. These headaches were generalized, occurred about every 3 days, and showed no tendency to increase in frequency or severity. During the onset of the symptoms he had noticed decreased sexual desire. This had progressed to complete loss at the time of admission.

Examination. There was bilateral primary optic atrophy, with markedly decreased visual acuity, measuring 20/200 in both eyes. Studies of the visual fields revealed a clearcut left homonymous hemianopsia (Fig. 10). Examination of the cranial nerves gave negative results otherwise. There were slight central facial weakness on the right, slight weakness of the right arm and hand, the grip being 45 as compared with 60 on the left, and slight increase in the right biceps reflex. Endocrine disturbances, though not conspicuous, were present. They consisted of complete loss of libido, polyuria, a rather pronounced gain in weight in the year previous to admission, slight loss of hair, smooth and silky skin, and somnolence (Fig. 11).

Perhaps the most constant symptoms are the loss of visual acuity, field distortions, and the X-ray findings already mentioned. An homonymous hemianopsia was an invariable feature in my series. From this one would anticipate the location of the tumor on one or the other side of the sella turcica. Vision may

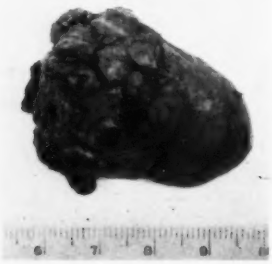


Fig. 11. Case 4. Meningeal fibroblastoma of lesser wing of sphenoid bone.

Fig. 12. Case 4. Complete oculomotor paralysis in a patient with a tumor of the lesser sphenoid wing.

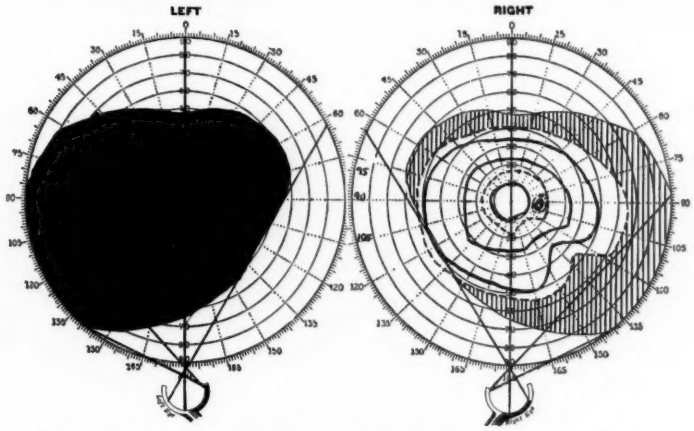


Fig. 13. Case 5. Fields before operation. Vision, left shadows, right 6/5−4 with correction.

be seriously impaired, and in all cases but one in my series there was a primary optic atrophy and in one instance a papilledema on the contralateral side and a primary optic atrophy homolateral to the lesion.

In 1 instance there was a complete oculomotor paralysis (Fig. 12). Among associated symptoms were noted impairment of taste, hypopituitary stigmas, impairment of memory, and homolateral paralysis which may be due to compression of the anterior and middle cerebral vessels.

The following case differs from the former in many particulars and is cited by way of contrast.

CASE 5. Middle aged man complained of pain on left side of nose for 3 years. Meanwhile he developed a left exophthalmos, left sided blindness, and corneal hypesthesia. The X-ray films revealed a destructive lesion of the lesser wing of the sphenoid, which at the operation proved to be, as suspected, a fibroblastoma. The tumor was readily removed.

Clinical history. H. E., aged 42 years (File No. 30181), was referred by Dr. T. H. Farrell of Utica, New York, to the Neurosurgical Service of the University Hospital, November 13, 1934. The patient was well until August, 1931, when he developed pain first in his left arm and then on the left side of the nose. It was a steady, constant ache. From April to October, 1932, he was pain free. Then his vision became "cloudy," he lost 20 pounds in weight, and felt slack. July, 1933, he noted spells in which he could not see or hear. By September, 1933, his vision in the left eye was much worse and the left eye became more prominent. December, 1033, an exploratory operation was performed in another hospital, and the operator reported thickened walls of the left orbit. No tumor was found.

The pain and failing vision continued and in April, 1934, he applied at another clinic for relief. Here his symptoms were thought to be of functional origin.

When he reported to my service the pain was still present and referred chiefly to the side of the nose. His left eye was amaurotic; he had lost some 40 pounds in weight and was quite demoralized.

Examination. The neurological findings were few and had to do only with the left eye. There was a marked exophthalmos, by measurement right 16.5, left 18.5; there was limitation of ocular movements (left); right eye vision, blind, left eye vision 6/5. Fields slight bitemporal cut (Fig. 13). There was impairment of corneal sensation (left).

Roentgenogram. Dr. Pancoast reported that either a portion of the lesser wing of the sphenoid bone had

Fig. 14. Case 5. Roentgenogram reveals destruction of the lesser wing of the sphenoid.

Fig. 15. Case 5. Tumor of lesser wing of sphenoid surrounding left optic nerve.

Fig. 16. Case 5. Photographs of patient 3 weeks after operation. Coronal incision imperceptible. Hypesthetic area outlined.

been removed, or that he would have to report there had been some destruction of this portion of the sphenoid wing (Fig. 14).

In all other respects the examination was negative.

With the prolonged history of pain referred to the left maxillary division of the fifth nerve, with the left exophthalmos, the left partial ophthalmoplegia, left blindness, and finally the X-ray evidence of destruction of the sphenoid wing, the diagnosis seemed obvious—fibroblastoma of the lesser wing.

Operation. November 20, 1934. The question of approach was complicated somewhat by the presence of the incision from the previous operation. This difficulty was met by using our "coronal" incision from the tip of one ear to that of the other. This flap included the earlier incision and proved a happy solution of what seemed a difficult surgical problem. The incision of the first operation would have been wholly inappropriate for our exploration. The tumor was exposed without any difficulty (Fig. 15). Beginning in the anterior fossa above the lesser wing and passing obliquely downward, completely surrounding the left optic nerve on its way, it extended into the middle fossa and stopped just over the gasserian ganglion.

The tumor was oblong in shape and rather nodulated on the surface. A greater portion, including the left optic nerve between the optic foramen and chiasm was scalloped out with the electrical loop and the capsule removed later by blunt dissection. The tumor was quite bloodless and easily excised. The dural incision was closed snugly, bone flap replaced, and scalp incision closed with tier sutures.

Postoperative course. The postoperative course was uneventful save for an aphasia which did not appear for 48 hours and lasted only 5 days. He was discharged 23 days after the operation. There was an hypesthetic area corresponding to the distribution of the first and second divisions of the trigeminal nerve (Fig. 16).

Pathological report. Fibroblastoma.

TABLE I.—SUMMARY OF FINDINGS IN FIVE CASES OF TUMORS OF THE LESSER SPHENOIDAL WING

Visual acuity	Optic atrophy	Papilledema	Fields	Roentgen findings	
				Measurements of sella turcica	Dorsum
Right eye 6/9 Left eye 6/4			Left homonymous hemianopsia incomplete	12 by 11 mm.	Rarefied
Both eyes 20/200	Bilateral primary		Left homonymous hemianopsia	12 by 6 mm.	Slight atrophy
Right eye, blind	Right eye primary	Left eye	Left inferior quadrantic cut		Complete erosion
Right eye 1/40 Left eye 2/40	Bilateral primary		Right homonymous hemianopsia	12 by 11 mm.	Negative
Left eye, blind	Unilateral primary		Left eye, blindness	Destruction lesser wing	

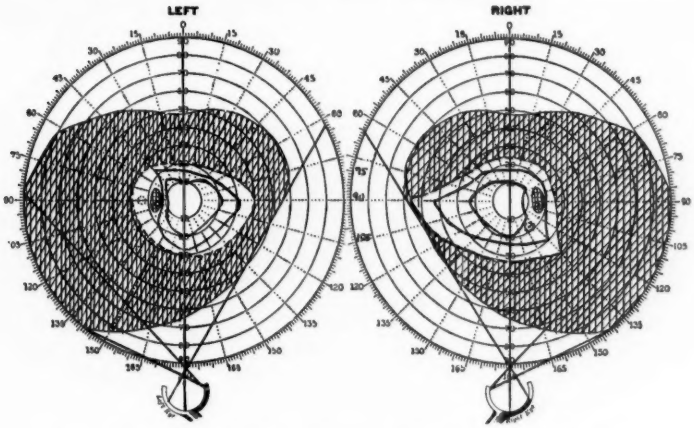


Fig. 17. Case 6. Fields before operation. Vision—left eye 6/9; right eye 6/9.

The symptoms in this case were distinctly unilateral and in that particular the case fits into our conception of these lesser wing tumors, but there were some unusual features that deserve mention. In the first place, all the symptoms were essentially focal; in the second place, there was an exophthalmos and partial ophthalmoplegia not usually observed. Again, the X-ray findings admitted of but one interpretation; instead of atrophy of the clinoid processes or erosion of the dorsum sellæ there was a definite loss of substance of the sphenoid wing. Finally, from the beginning and for 3 years the conspicuous symptom had been pain, pain referred to the trigeminal distribution especially that of its second division. Strangely enough the true nature of the lesion had not been recognized until the patient reported to this clinic. By this time optic atrophy was so well advanced that the vision of his left eye could not be restored.

Generally speaking these lesser wing tumors may be distinguished from suprasellar lesions by the conspicuously unilateral picture. It is not pertinent in this discussion to consider their differentiation from tumors arising from the greater wing of the sphenoid bone. (See "Parasellar Tumors," Alpers and Groff.)

GROUP IV. SUPRASELLAR PSEUDOTUMORS

Under the caption "Cerebral Pseudotumors," I reviewed in 1930 a series of 22 cases in which the symptoms mimicked those of a solid lesion but were found to be due to a circumscribed collection of fluid beneath the arachnoid. Of these 22 cases, 4 suggested an hypophyseal, and 1 a suprasellar lesion. The term "pseudotumor" was first employed by Nonne and since then has been variously referred to as "meningitis serosa," "meningitis serosa circumscripta," "meningo-encephalitis serosa," "arachnitis," and "generalized cisternal arachnoiditis." Since the pathological lesion may vary, and since in a number of cases, in fact in most recorded as pseudotumor no histological studies of the arachnoid

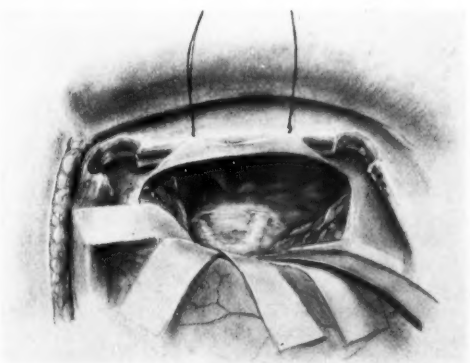


Fig. 18. Pseudotumor in the suprasellar area showing a thickened arachnoid membrane over the optic nerves and chiasm, giving rise to symptoms of a chiasmal syndrome.

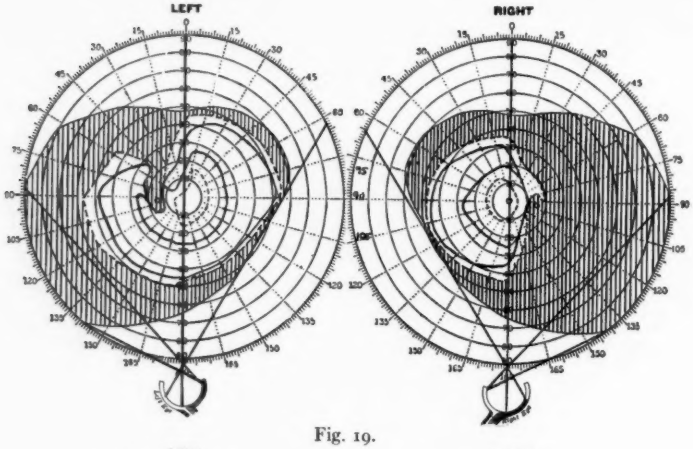


Fig. 19.

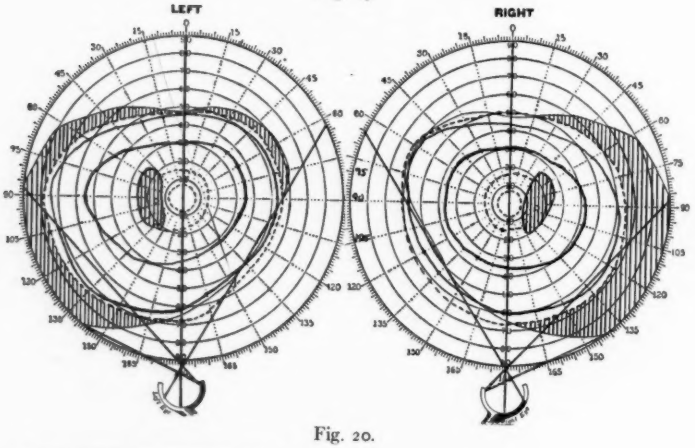


Fig. 20.

Fig. 21.

Fig. 19. Case 7. Fields before operation. Vision—left eye, 6/22? right eye, 6/22?
Fig. 20. Case 7. Fields after operation. Vision—left eye, 6/15; right eye, 6/15.
Fig. 21. Case 7. Photograph of patient on discharge from hospital.

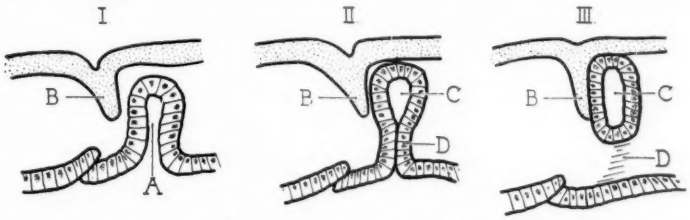


Fig. 22. Diagrammatic sketch of the development of the hypophysis from the buccal cavity. I, The original invagination from the buccal cavity *A*. II, Communication with the buccal cavity, obliterated at *D*, the structure from which the anterior lobe arises, *C*. III, The remnant of stalk, *D*, the anterior lobe, *C*, in close relation with the infundibular process, *B*.

were made, it seems that Nonne's term "pseudotumor" is more descriptive and should be retained.

Case 6. I. S., aged 49 years, female (File No. 13735) was first admitted to the Neurosurgical Service of the University Hospital June 19, 1928, and readmitted November, 1928, December, 1928, and April, 1930.

Clinical history. In 1920, 8 years ago, she first noticed that her vision was failing. She could read fine print at this time but was unable to see objects either to the right or left. Evidently at that time she had a bitemporal hemianopsia. Her ethmoid sinuses were drained, but without any effect upon her fields or her visual acuity. In 1928, she was told her fields were becoming more restricted (Fig. 17). Her vision November, 1928, was 6/9 in each eye. There was no papilledema.

April, 1930, on readmission to the University Hospital there was some loss of her olfactory sense; vision, reduced to tubular type, was right eye 6/15 and left eye 6/22. In all other respects her examination was negative.

Operation. May 12, 1930, transfrontal craniotomy, right. Under local anesthesia. Quoting from the operation notes: "There was no evidence whatsoever of a tumor either above or below the chiasm. The naked eye appearance was very much that which we have already described in other cases of pseudotumor. The arachnoid seemed quite adherent over the chiasm and at places thickened. One might well understand how the cerebrospinal fluid could be more or less pent up over the chiasm and give rise to pressure symptoms." The operative diagnosis was suprasellar arachnitis.

It is interesting to note that before the patient's discharge from the Hospital, the fields had expanded and were three times as large as

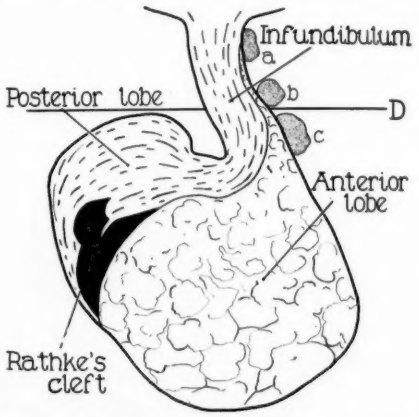


Fig. 23. Anatomical drawing to show the various constituents of the fully developed hypophysis. Note between the anterior lobe and the posterior lobe the location of Rathke's cleft.

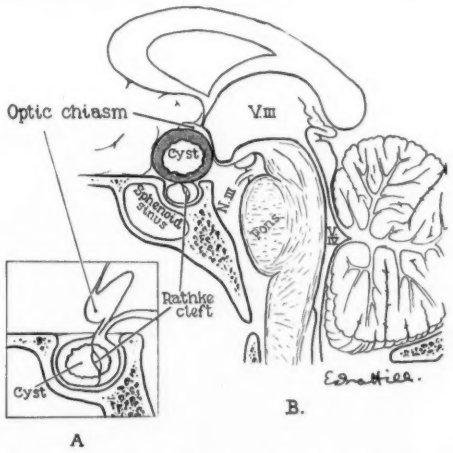


Fig. 24. A, Intrasellar Rathke cleft cyst compressing anterior and posterior lobes but causing no enlargement of sella. Note the origin from the Rathke cleft. *B*, Suprasellar Rathke cleft cyst similar in origin to inset *A* with compression of optic chiasm and only minor sellar changes

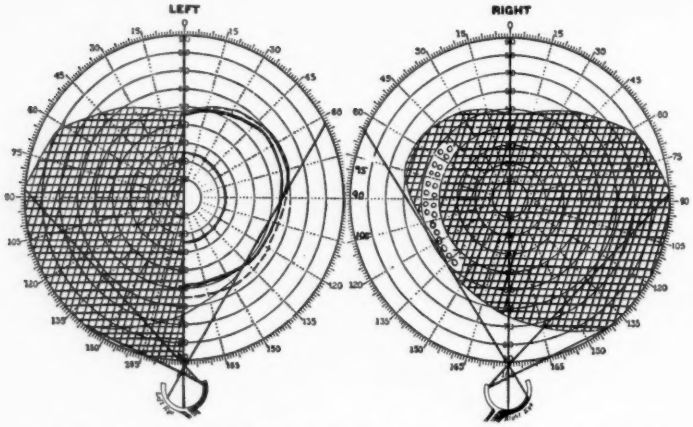


Fig. 25. Case 8. Fields before operation. Vision—left eye, 3/60; right eye, shadows.

before the operation. May, 1934, when last heard from, the fields were reported as wider than on the previous examination.

My experience with the surgical treatment of pseudotumor or arachnoiditis has been most satisfactory, at least to the extent that with one exception I have in no instance been called to operate a second time.

The etiology of this condition is obscure. One may postulate a focus of infection, as in the case above cited, when the patient had had an ethmoiditis but in most instances infection does not seem to have been a factor. The diagnosis must finally be verified by the operation

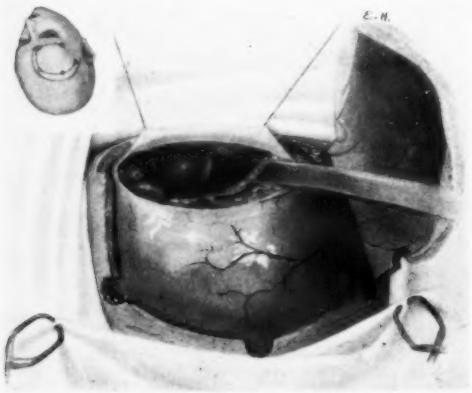


Fig. 26. Case 8. Drawing at operation. Tumor of Rathke's cleft.

findings, thickening of the arachnoid with adhesions, and a circumscribed collection of fluid in the cisterna chiasmatis (Fig. 18).

In addition to the increased amount of fluid in the cisterna chiasmatis I have found the optic nerves surrounded and constricted by the thickened pia arachnoid and have made incisions in the membrane to relieve the constriction.

From the standpoint of diagnosis one must depend largely upon the visual phenomena, the loss of visual acuity, and the field distortions, and hemianopsia or, as in the preceding case, a concentric contraction of vision. This patient, however, may in the first instance have had a bitemporal hemianopsia as at first she was unable to see objects in either temporal field. The provisional pre-operative diagnosis may be quite reasonably a suprasellar fibroblastoma. I know of no means of differentiating a suprasellar fibroblastoma from a suprasellar arachnoiditis unless it be by means of an encephalogram. In the latter case the cisterna chiasmatis may be enlarged, should the spaces not be entirely shut off by adhesions, and in the former the cistern would not be portrayed.

The following case is of no little interest because the symptoms were only of 6 months' duration and the sella turcica was definitely enlarged. The picture would have been readily explained by a pituitary adenoma.

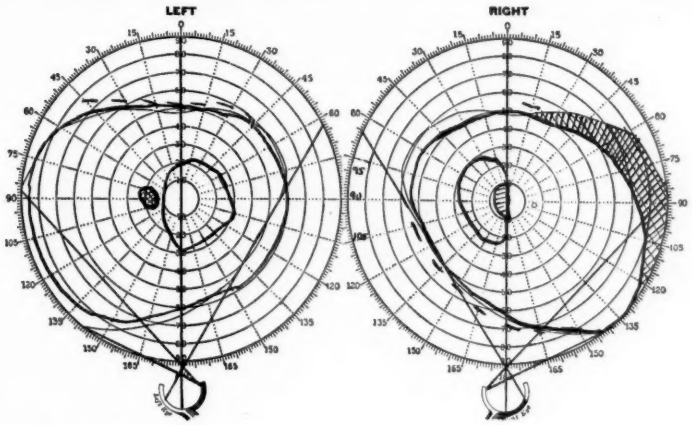


Fig. 27. Case 8. Fields after operation. Vision—left eye, 6/12 with correction; right eye 6/60 with correction.

CASE 7. A woman in her 38th year had symptoms for only 6 months; bitemporal hemianopsia, impairment of vision, headache, vomiting and vertigo, and an enlarged sella turcica film completed the picture. Operative findings, pseudotumor. Immediate relief.

Clinical history. L. M., aged 38 years (File No. 30009), was admitted to the Neurosurgical Service, referred by Dr. Edward Lentz, October 15, 1934, with the following history:

From March, 1934, 6 months, she has had shooting pains in the occipital region and a sense of fullness in the head. At times she became dizzy and had to sit down. July, 1934, the headache, once intermittent, became constant. Attacks of nausea and vomiting followed. She complained that though she could see the printed word she could not grasp the meaning.

Examination. There were no objective findings save the field distortion and the X-ray picture.

There was a complete loss in the temporal field of vision in right eye and of the upper temporal quadrant in left eye. Vision in both eyes was 6/22. Discs appeared normal (Fig. 19).

Roentgenogram. Definite enlargement of the sella turcica (14 by 11 millimeters) with encroachment upon the sphenoid sinus but without atrophy of the posterior clinoid processes. The findings suggest a pituitary tumor.

All other special examinations were negative.

Operation. November 5, 1934. Transfrontal craniotomy, right, under local anesthesia. In approaching the pituitary fossa along the sphenoidal ridge it was evident there was no pituitary tumor. A bluish membrane overlay the chiasm and optic nerves and confined beneath it and around the optic nerves was a large collection of fluid. The membrane, presumably thickened arachnoid, was removed and the wound closed.

Operative diagnosis. Pseudotumor.

Postoperative course. The patient's convalescence was uneventful. Save for 2 days of drowsiness that often follows the pituitary exploration, the convalescence was uncomplicated. Particularly striking was the widening of the fields within 2 hours of the operation and upon the patient's discharge, November 17, 12 days after the operation, the fields were nearly normal (Fig. 20) and her vision was both eyes 6/15. The headaches had disappeared (Fig. 21).

When there are signs of hypophyseal dysfunction one may consider with perfect propriety a suprasellar adenoma. Such was the case in a patient (File No. 2759 N.S.) who had obesity, evidence of femininity, a basal metabolism of minus 22, and an homonymous

Fig. 28. Case 8. Photograph of patient 3½ years after operation.

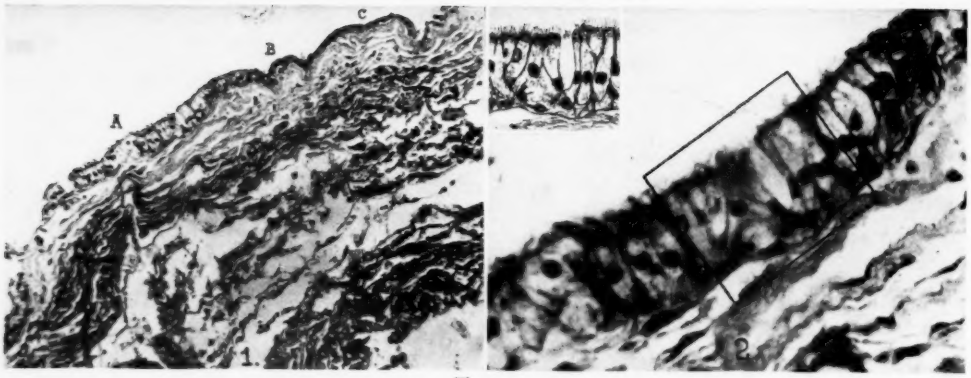


Fig. 29.

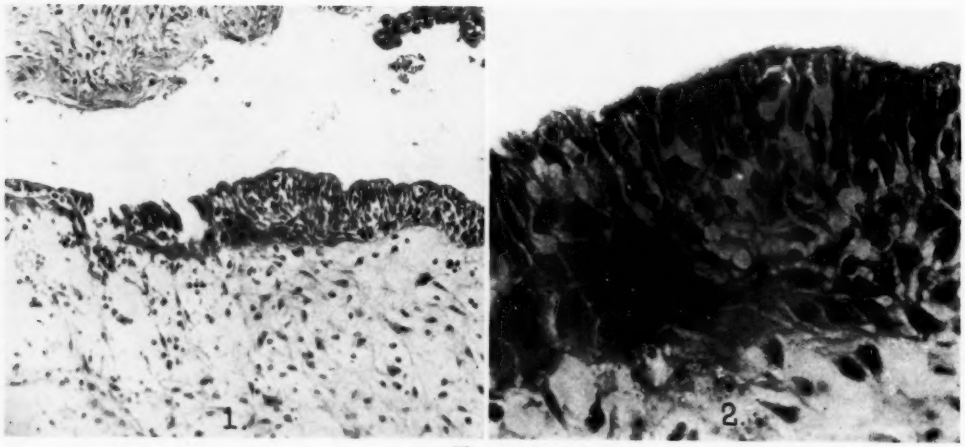


Fig. 30.

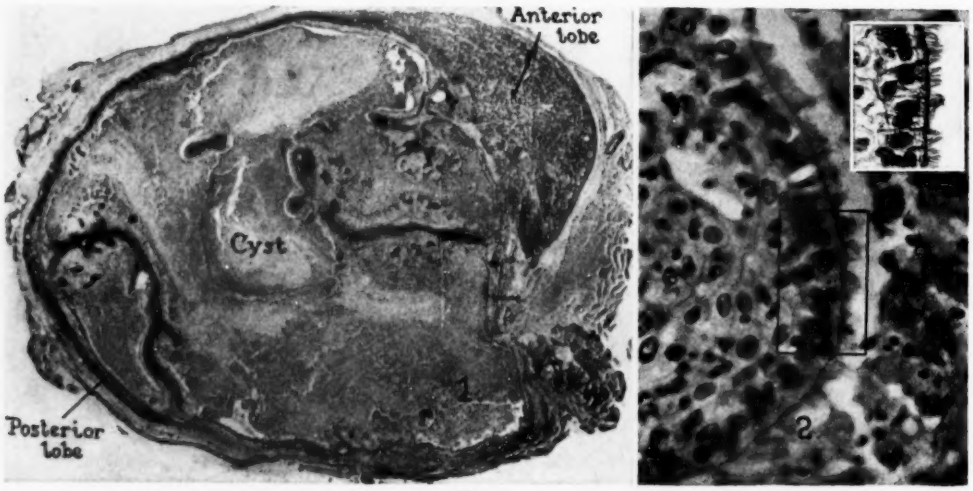


Fig. 31.

hemianopsia. The case proved to be one of pseudotumor. No tumor was found at operation and the end-results have been most gratifying. At least, April 4, 1930, 6 years after the operation his vision was right eye 6/15, left eye 6/9, as compared with right 1/60 and left 4/60 before the operation. He said he felt better than he had for 21 years. He weighed at the time of operation 210 pounds and at the time of this report, 213 pounds.

Briefly, then, suprasellar arachnoiditis may be said to be characterized by failing vision, optic atrophy, an hemianopsia or concentric contraction of fields, usually with no enlargement of the sella turcica, but in some instances with signs of hypophyseal dysfunction.

GROUP V. TUMORS OF RATHKE'S CLEFT

There is good reason for the recognition of a separate group of tumors to be known as the tumors or cysts of Rathke's cleft. In the past the term "Rathke pouch tumor" has been used loosely to designate almost any congenital suprasellar tumor, and chiefly for the hypophyseal stalk tumors. The term so used is obviously a misnomer, for the stalk tumors are not truly tumors of Rathke's pouch or of its adult counterpart, the Rathke cleft in the adult human hypophysis.

The term "Rathke's pouch tumor" for obvious reasons, as we shall see later, should give way to "Rathke's cleft tumors." In this brief communication we shall endeavor so to define the Rathke's cleft tumor anatomically and pathologically that it may be identified and acknowledged as a definite pathological entity and may be differentiated from any other hypophyseal or parahypophyseal lesion.

Rathke's pouch in the terms of the anatomist is an invagination from the roof of the primitive oral cavity. In the process of development it becomes constricted off and a sac is formed with a narrow stalk (Fig. 22). The sac eventually closes and the stalk, originally connected with the mouth, usually disappears. This stalk in some cases persists, as does the thyroglossal duct—the analogy is quite close—and from the epithelial rests the stalk tumors have their origin.

The original Rathke's pouch becomes converted into a solid structure, the pars anterior or the glandular lobe of the hypophysis. But there remains between the pars anterior and the pars posterior or processus infundibuli *a small cleft* (Figs. 23 and 24). *This is all that remains of the original pouch, as described by Rathke, and it is from this cleft that the tumors we discuss originate. In this sense it would seem proper to designate them as Rathke's cleft tumors.*

For purposes of illustration, we present the following case:

CASE 8. The patient, a male of 52 years, had had frontal headaches and eye trouble for 2 years. Blindness of the right eye for 4 months. Temporal hemianopsia in left eye. Blurring of discs. Erosion of right sphenoidal ridge. Transfrontal craniotomy with disclosure of cyst presenting between optic nerves. Histologically a true Rathke's cleft cyst with columnar ciliated epithelial lining.

Clinical history. C. B. (File No. 22337) was referred to the Neurosurgical Service of the University Hospital July 27, 1931, by Dr. R. D. Wallace. About 2 years before his admission he began to have frontal headaches. He was treated for sinus disease and in 11 weeks his headaches disappeared. They returned 8 months before his admission to the hospital and persisted from this time on. They were dull, constant and mostly frontal, though for 2 months before entrance into the hospital he had pain in the left temple.

In 1929, about 2 years before admission, he began having trouble with his eyes. Objects were at first blurred and indistinct. His vision became steadily worse until he lost it completely in his right eye 4 months ago.

Examination revealed total blindness of the right eye, temporal hemianopsia in the left (Fig. 25) and yellow optic discs which were blurred along their margins. There were no other positive findings. The spinal fluid pressure was 150 millimeters of water. The blood and spinal fluid serology were entirely negative.

Roentgen observations. The roentgenogram of the

Fig. 29. Left, A portion of the cyst wall showing the ciliated columnar epithelium, *A*, with transition to unciliated cuboidal, *B*, and flat cells, *C*. Hematoxylin and eosin stain. Right, A high power view showing the stout cilia projecting from the columnar cells. Hematoxylin and eosin stain.

Fig. 30. Left, Transition epithelium of a pseudosquamous type in the cyst wall. Hematoxylin and eosin stain. Right, The same area under higher power showing the tendency to stratification and squamous-like cells in the lower layers. Hematoxylin and eosin stain.

Fig. 31. Case of Fulstow. Left, A large Rathke cleft cyst of the intrasellar type compressing the anterior and posterior lobes, particularly the latter. Right, Part of the cyst is lined with a ciliated columnar epithelium.

skull showed some erosion of the right sphenoidal ridge. The pituitary fossa measured 11 by 8 millimeters and showed no erosion or enlargement.

Operation. July 29, 1931. Right transfrontal craniotomy, avertin anesthesia. The usual dual flaps were reflected as for pituitary exploration. It was apparent that there was an increased intracranial pressure and, as the frontal lobe was elevated, an unusual amount of cerebrospinal fluid was evacuated. This so reduced the pressure that a clear view could be had of the whole anterior fossa from right to left. Presenting between the optic nerves was a bluish membrane, evidently a cyst wall (Fig. 26). This was readily freed from both the right and left optic nerves and 8 cubic centimeters of a brownish fluid was evacuated from the cyst cavity. With this the cyst walls collapsed, leaving a considerable space between them and the optic nerves. The chiasm was displaced backward and the distance from the optic foramina to the chiasm was at least 3 centimeters (Figs. 27 and 28).

The walls of the Rathke's cleft cyst usually are lined with a columnar epithelium from the full surface of which there project stout cilia, usually several from one cell (Fig. 29). The cytoplasm of these cells is similar to that of the goblet cells but contains no mucin. It is quite vacuolated and mucoid-like. The nucleus usually at the bottom of the cell, is round, heavily chromatinized, and single. There are basal bodies at the base of the cilia. This columnar epithelium may be followed into transitional cuboidal and flat cells neither of which possess cilia. Some times there is in the tumor wall a poorly developed squamous epithelium (Figs. 30 and 31), suggesting the possibility of a transition of these cysts into the stalk tumors. The rest of the tumor is composed of a vascular and fibrous bed, the latter of rather stout proportions.

It may be that these cysts are not always lined with a ciliated epithelium. There is an occasional thin walled cyst lying in the suprasellar region which is lined with a flattened cell similar to the type of cell seen in the transition areas of the ciliated cyst. Due to the pressure of fluid within the cyst, it is quite possible that the cells, originally ciliated and columnar, have lost their cilia and become flattened.

The evidence for the origin of these cysts from the remnants of the Rathke pouch lies in the finding of Duffy that the Rathke cleft cysts are lined by a cylindrical epithelium which is often ciliated, and in the fact that ciliated cells in the Rathke cleft of the adult hypophysis are found in a small proportion of cases, about 1 in 50 or less. Ramussen found them in only 2 of 300 hypophyses. The origin of these ciliated cells is not very clear. However, we believe that from such cells may be traced the origin of the tumor which we designate as a Rathke cleft cyst.

Only 1 such tumor has been found in my series of hypophyseal tumors (see Case 6), but it is probable that more will be disclosed now that we have a more precise idea of their nature. Theoretically, cysts of Rathke's cleft should be found within the sella because of the position of the cleft remnant between the anterior and the posterior lobes. Such a cyst has been described by Fulstow who found a large cyst in the hypophysis between the anterior and posterior lobes in a man of 48 with glandular symptoms but no ocular manifestations. The hypophysis was about three times normal in size. The cyst within it was lined with stratified squamous epithelium with long papillary projections on which a low ciliated columnar epithelium could be seen. Some of the cells contained mucin. In all its characteristics, except for the papillary projections, the cyst resembles the cyst for which we have reserved the term Rathke's cleft cyst. Such cysts may not be rare, and it is possible that the simple cysts of Duffy, for example, fall into this group. Hortega describes microscopic cysts lined with a cylindrical epithelium which may be ciliated or non-ciliated and he too believes these cysts are derived from Rathke's pouch. We urge that the term Rathke pouch tumor be abandoned and for the reasons given the term Rathke's cleft cyst be substituted.

It should be quite apparent that in many instances it will be quite impossible to determine by the clinical picture, before the operation, what the nature of the lesion may be. One might readily mistake a Rathke's cleft tumor for a primary hypophyseal tumor, should the cyst be intrasellar, or for an extrasellar adenoma should the cyst not be contained within the confines of the sella turcica. At the operation the Rathke's cleft lesion will be found to be prechiasmal and cystic in character.

GROUP VI. HYPOPHYSEAL STALK TUMORS

In the classification we have adopted of lesions that are indirectly related to the hypophysis, what we have chosen to designate "hypophyseal stalk" tumors constitute a not inconsiderable number and these may be differentiated from the preceding group, the "hypophyseal cleft" tumors, by certain pathological and clinical characteristics. For illustration we have selected 4 cases from our series.

In the first case, a boy of 16 years (File No. 19387) with the stature of a 10 year old child, the outstanding features were arrest in growth, convulsions, somnolence, headache, defective vision, primary optic atrophy, a bitemporal hemianopsia; the roentgenogram revealed atrophy of the dorsum sella and convolutional atrophy, the floor of the sella was markedly depressed and there was the shadow of a calcified tumor suprasellar.

In the second case, the patient, a child, though in her eighth year, was said to have had headache since she first was able to talk. There were no neurologic signs save an abortive bilateral ankle clonus. Of hypophyseal stigmas a tendency to adiposity, including a protruding abdomen, prominent breasts, and tapering fingers were readily recognized. The basal metabolism was minus 6. The right eye was amaurotic and the temporal field of the left eye was obscured; the discs had the appearance of a subsiding choking with atrophy; they were gray with obscured margins. In the roentgenogram the clinoid processes had disappeared, the floor of the sella was eroded, the sella turcica was somewhat enlarged, and above and behind was a calcified shadow 4 by 6 centimeters in diameter.

In the third case, the predominant symptoms were those of increased intracranial pressure, headaches, projectile vomiting, and papilledema. There were no sensory, motor, or reflex phenomena. There was convolutional atrophy but no apparent involvement of the sella turcica. Vision in the right eye was 6/21, in the left 6/12 and the discs showed a papilledema of plus 5 diopters. The fields were normal. The child, aged 12 years (File No. 9169), was short for her years, there was evidence of adiposity, the basal metabolism was minus 4. A year after a subtemporal decompression the child suddenly died and a large calcified tumor was found extending from the anterior prefrontal space to the anterior margin of the pons.

The first three cases cited were those of children, 8, 12, and 16 years, respectively, and the fourth is included because of the contrast in ages. This patient, a woman in her thirty-third year (File No. 10028) had complained of headache for over a year. Her symptoms might readily have been cited as those of an hypophyseal adenoma: amenorrhea, adiposity, basal metabolism minus 15, a bitemporal hemianopsia with deteriorating vision (2/60), but the sella turcica was not enlarged. A cystic tumor beneath and behind the optic chiasm was found and removed and the patient is alive and well 8 years later.

Altogether there are in our files 16 cases of these so called hypophyseal stalk tumors. The *life history* of these tumors has a wide range. In about half it was a matter of months, from 4 to 10, and in the others a matter of years, from 1 to 7. For example, in 1 of the cases cited (Case 2), a child of 8 years, the patient had complained of headache since she was old enough to talk. In another (Case 1) the child had had headache and somnolence for 3 years, and his growth from the beginning had been arrested. The first symptom in 6 cases was headache, in 2 headache and dimness of vision, in 1 headache and somnolence, in 1 dimness of vision, in 3 arrest of growth, and in 1 convulsions.

The *basal metabolism*, when recorded, was always subnormal. In fact, in the vast majority of lesions, when hypophyseal function is disturbed, the metabolic rate is below rather than above normal. This applies even to primary hypophyseal adenomas. Hence, the metabolic rate is of little or no significance in the differentiation between parahypophyseal and primary hypophyseal lesions.

As to the *sex* and *age* it so happens that two-thirds of our patients were males. This is a matter of little significance. But, as to age, one would expect when dealing with lesions arising from congenital anlage, that the majority of patients with stalk tumors should be children or adolescents. This supposition is quite in conformity with the facts. Of 14 cases analyzed, 9 were between the ages of 7 and 17, 2 were in the third decade, 2 in the fourth decade, and 1 in the sixth. For purposes of comparison, remember that 70 per cent of the stalk tumors developed in patients under 20 years of age, whereas 84 per cent of the same number of adenomas were found in patients over 20 years of age. Age, therefore, may give a clue to the differential diagnosis of the various groups of tumors in this region, if it be accepted that the majority of stalk tumors appear in children, that adenomas are unusual before the twentieth and suprasellar fibroblastomas before the thirtieth year.

When considering the *visual disturbances* of stalk tumors, one must bear in mind the location of the anlage from which these tumors originate. When tumors arise from the lower

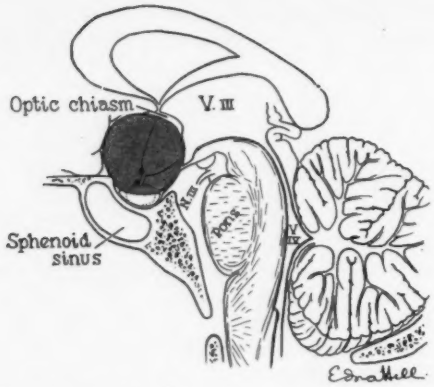


Fig. 32. Hypophyseal stalk tumor arising from lower rest eroding the sella, compressing the optic chiasm and nerves.

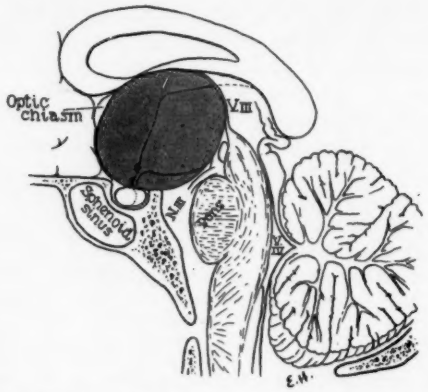


Fig. 33. Hypophyseal stalk tumor, chiefly retrochiasmal, arising from upper cell rest, invading third ventricle, compressing optic chiasm, slightly eroding sella.

epithelial anlage (Fig. 32), one finds a primary optic atrophy and when from the upper epithelial anlage, a papilledema with a secondary optic atrophy. It is not always possible to determine at the operation from which of these two anlagen the tumor arises, but we have assumed that when the tumor was prechiasmal the tumor arose from the lower anlage and when retrochiasmal, from the upper anlage (Fig. 33). This would seem to be borne out by the facts. In all cases but one of primary optic atrophy the tumor presented prechiasmally and in most (5 of 7) of those described as retrochiasmal there was a secondary postpapillitic atrophy.

As to the *visual fields* of 7 tumors prechiasmal, the fields were described as follows: 3, temporal hemianopsia of one eye; 1 concentric contraction; 1 bitemporal quadrantanopsia; and 2 bitemporal hemianopsia. Whereas of 6 tumors manifestly retrochiasmal, the fields were as follows: 1 binasal hemianopsia; 1 barrel vision; 1 normal fields; and 2, homonymous hemianopsias.

Summarizing the various fields of the entire series of stalk tumors there were:

Temporal or bitemporal hemianopsias	6
Bitemporal quadrantanopsia	1
Homonymous hemianopsia	2
Binasal hemianopsia	1
Concentric contraction	2
Normal fields	1
Amaurosis	1
	14

As one might anticipate, because of the proximity of the stalk tumors to the sella turcica and the resulting pressure on the hypophysis, *endocrine disturbances* of one kind or another form part of the clinical picture (see Table II).

These endocrine disturbances are more constant in the younger than in the older patient. The most common of them was arrest of growth and the next most common somnolence. In addition to dwarfism (7) and somnolence (6), there may be adiposity (5), sexual defects (4), femininity (4), polyuria (3), amenorrhea (1), and emaciation (1). Generally speaking, the endocrine features are those of the Froelich type. Gigantism or acromegaly were conspicuous by their absence.

One might anticipate signs of *intracranial pressure* when the tumor encroaches upon the third ventricle and establishes a ventricular block; hence, headache, vomiting, and papilledema. Headache and vomiting were common to all, whereas papilledema was observed only three times in the series.

One must divine the effects of indirect pressure, such as headache, vomiting, and papilledema and secondary optic atrophy, from that of direct pressure, primary optic atrophy. Again, we must presume that tumors from the upper anlage are more prone to cause ventricular blocks with consequent increased intracranial pressure, whereas tumors from the

TABLE II.—THE INCIDENCE OF ENDOCRINE DISTURBANCES WITH RELATION TO AGE

Case	Age	Dwarfism	Somnolence	Adiposity	Sexual defect	Femininity	Polyuria	Amenorrhea	Emaciation	
1	7	plus					plus			Under 20 years of age
2	8			plus						
3	9		plus	plus	plus	plus				
4	12	plus	plus			plus				
5	12	plus		plus						
6	15	plus	plus		plus		plus		plus	
7	15	plus			plus					
8	16		plus		plus					
9	17	plus				plus				
10	25		plus							Over 20 years of age
11	28		plus	plus		plus				
12	33							plus		
13	38									
14	50			plus			plus			

more lower anlage direct pressure and primary optic atrophy.

There are in a few instances associated or *neighborhood symptoms*, and here and there symptoms of extraneous origin not related to either the hypophysis, the discs, or the fields. In this category are included visual hallucinations (3), auditory hallucinations (1), deafness (3), tinnitus (1), vertigo (1), diplopia (1), loss of associated movement (1), inequality of pupils (1), and, in several, signs of frontal lobe invasion, such as defective memory, psychosis, delusions, jocularity, irritability, viciousness, mental apathy, and depression.

Because of the varying location of these tumors along the stalk with relation to the sella turcica *the roentgenograms* present various pictures. Thus, the sella turcica was moderately enlarged (4), markedly enlarged (4). There was atrophy of the dorsum sellæ, moderate (6) or marked (5). Convolutional atrophy (4) was an indication of prolonged intracranial pressure. The most significant X-ray evidence, as concerns the differential diagnosis, is calcification. Calcification was noted in half of the series and the resulting shadows may appear as irregular areas scattered throughout the tumor or as a marginal shadow following the outline of a calcified cyst wall. This combination—calcified shadows, endocrine disturbances, field distortions with alterations of the discs—especially in young people bespeaks with reasonable certainty a stalk tumor.

The following are 4 illustrative cases referred to in abstract at the beginning of the section on hypophyseal stalk tumors.

CASE 9. *Summary.* Always undeveloped, the patient was admitted in his sixteenth year. Somnolence, headache, ptosis (left), and convulsions were the outstanding symptoms. At operation a large cystic tumor was revealed.

Clinical history. C. M., a boy, aged 16 years (File No. 19387), was admitted to the Neurosurgical Service of the University Hospital on June 18, 1930. His father was subject to convulsions; his mother was living and well; there were no brothers or sisters. He had always been underdeveloped. Three years previously, he became backward in school, refused to study, complained of headache, and was sleepy most of the time. One year before admission, vision began to fail. In April, 1930, he had three convulsions, in each of which he lost consciousness.

Neurologic status. Though 16 years of age, the child's stature was that of a boy of 10 years (Fig. 34). There were no neurologic signs other than ptosis of the left eyelid. There were no hypophyseal stigmas other than arrested growth, and at times somnolence.

Ocular disturbance. Vision in the right eye was 6/60; in the left eye, 6/30. The fields showed bitemporal hemianopsia. Primary optic atrophy was present.

Roentgen observations. There were convolutional atrophy, with widening of the sutures; the shadow of a calcified tumor (Fig. 35), and almost complete atrophy of the dorsum sellæ and the posterior clinoid processes. The floor of the sella was markedly depressed.

Metabolism. The basal metabolic rate was minus 37.

August 26, 1930, the patient was readmitted in a state of stupor. Dr. Grant removed 20 cubic centimeters of a dark brown fluid from the cyst, without any relief. Dehydrating agents seemed of no avail, and the patient lingered in a state of unconsciousness for 8 weeks and died on October 6.

Pathological report. The tumor extended from the frontal lobes to the pons (Fig. 36). It was almost completely calcified and cystic. The middle cerebrals had been compressed with resultant softening of the cerebrum on both sides. Histologically this was a typical stalk tumor, similar in its characteristics to the other tumors except that the cyst formations were very numerous and calcification was extremely extensive, involving almost all parts of the tumor.

CASE 10. A girl, aged 8 years, had had daily headaches for years; in the past month vision had almost failed, and for 8 days headache had been intense and vomiting incessant. A large calcified tumor was found and in part removed. The patient was discharged 12 days after operation.

Clinical history. L. E. H., a girl, aged 8 (File No. 7042 N. S.), was referred to the neurosurgical clinic by Dr. J. L. McKee, on November 13, 1925. The mother said that the child had had a headache every day since she could talk. The attacks lasted about an hour and a half, and little attention was paid to them. But for the 8 days preceding admission the headache had been intense and vomiting incessant. For a month vision had been failing, until at the time of admission the child could not recognize her playmates.

Neurologic status. Apart from an abortive ankle clonus on both sides, there were no neurologic signs except those to be recorded.

Hypophyseal stigmas. There was a tendency to adiposity, protruding abdomen, prominent breasts, and tapering fingers. The basal metabolic rate was minus 6.

Ocular disturbances. The left eye showed a temporal hemianopsia; vision was limited to counting fingers. The right eye was blind. The discs had the appearance of a subsiding choking, with atrophy; they were gray with blurred margins.

Roentgen observations. There were destruction of the clinoid processes, erosion of the floor of the sella, and some enlargement of the sella. A large calcareous deposit was seen extending backward and upward; it was about 4 centimeters in diameter.

Craniotomy. On January 13, 1926, a transfrontal craniotomy was performed on the left side. On reflection of the flap, the dura was exceedingly tense, but fortunately a dilated ventricle was found and with its evacuation the pressure was entirely relieved, so much so that the frontal lobe of its own weight fell away sufficiently to expose the region of the chiasm.

The tumor was readily seen, presenting prechiasmally. The left optic nerve, first seen, was on the stretch and ribbon-like. The center of the tumor seemed cystic, and about 1 cubic centimeter of fluid was evacuated. Through a capsular incision the cavity was curetted, but little tissue was recovered. The capsule was then freed from the chiasm and optic nerves, and as much as could be easily detached was removed. When finished, there presented in the sella a cavity, measuring approximately 2 by 2.5 centimeters in diameter.

Postoperative course. In the convalescent period vomiting persisted. The child did not react well. The general condition was not especially satisfactory, and on January 25, 12 days after the operation, the child was taken home. The asthenia continued, and the child died on February 1.

Histological report. The tumor was a typical stalk tumor with a well defined ameloblastic layer, extensive stroma, and calcium deposits. Spicules of calcium were found scattered through the tumor. No formation of bone was seen anywhere. There were rather extensive areas of degeneration everywhere throughout the tumor, chiefly in the stroma. No glial tissue was found.

CASE 11. A girl, aged 12 years (File No. 9169), was under observation for a year with signs of increased intracranial pressure and atrophy of the dorsum sella, headache, vomiting, choked discs and arrest of growth and adiposity. Subtemporal decompression with temporary relief. With recurrence of symptoms the patient died suddenly 2 days after readmission. A large stalk tumor (adamantinoma) was found at autopsy.

Clinical history. A. G., a girl, aged 12 (File 9169), was referred to the neurosurgical service of the University Hospital by Dr. L. F. Appleman, on September 15, 1926. For the ten months preceding admission the child complained of headaches, at first not severe and only once a month. On the day before admission it was discovered at the Wills Eye Hospital that she had choked discs, and she was referred to this service. Apart from projectile vomiting, of 6 months' duration, there had been no symptoms.

Neurologic status. With regard to the motor and sensory mechanism, examination gave entirely normal results. There were no signs suggesting a lesion either of the cerebral or of the cerebellar hemispheres.

Endocrine stigmas. The child was short for her age. There was a tendency to adiposity, with a protuberant abdomen and prominent breasts (Fig. 37). The basal metabolic rate was minus 4.

Roentgen observations. These showed convolutional atrophy without enlargement of the pituitary fossa (Fig. 38).

Ocular disturbances. The fields were practically normal. Vision in the right eye was 6/21; in the left eye, 6/12. Papilledema in both eyes measured 5 diopters.

As there was no positive evidence of an hypophyseal lesion and there were highly choked discs, the indication for a subtemporal decompression seemed clear.

Subtemporal decompression. This operation, preceded by a ventricular estimation (by Dr. F. C. Grant), was performed on September 24. Only 15 cubic centimeters of fluid obtained from the left ventricle and 8 cubic centimeters from the right. Apparently there was no hydrocephalus.

Postoperative course. Convalescence was uneventful, and the patient was discharged on October 4. At that time the papilledema measured 4 diopters in the right and 3.5 diopters in the left eye. Three months later the child was readmitted to the hospital and while under observation suddenly died with signs of medullary compression.

Autopsy. At autopsy a large tumor was found at the base of the brain with all the characteristics of a stalk tumor (Fig. 39).

CASE 12. A well developed woman, aged 33 years, had complained of headaches for over a year. There were a bitemporal hemianopsia and amenorrhea, but the sella turcica was not enlarged. Eight years after the removal of a cystic tumor beneath and behind the chiasm, the patient was well. Benefit followed the administration of thyroid extract.

Clinical history. K. A. K., a woman, aged 33 years (File No. 10028), was referred to the neurosurgical service of the University Hospital by Dr. Raymond H. Bloss and Dr. William G. Spiller, on December 16, 1926. The previous medical and family history was unessential. In October, 1925, the patient began to have headaches, at first dull but constant, later becoming very severe and occurring at intervals of several days. They were referred to the midfrontal region, with much pain over the right eye. In June, 1926, she suddenly became aware of failing vision and in August, she had the first vomiting spell. On one occasion she had diplopia. On December 4, vision became much worse and on December 5, for the first time she was unable to read. She had been receiving courses of roentgen treatment, but the fields continued to contract and the sight to fail.

Neurologic status. The patient was well developed and moderately obese. Her average weight for the past 10 years had been from 150 to 155 pounds (68 to 70 kilograms). There were no sensory or motor disturbances. The reflexes were normal.

Cerebrospinal fluid. The pressure was 182 millimeters; the fluid contained 4 lymphocytes; the Wassermann reaction was negative. Globulin was not increased.

Roentgen observations. The pituitary fossa measured 10 millimeters in the anteroposterior and 5 millimeters in the vertical plane (Fig. 40).

Hypophyseal stigmas. The basal metabolic rate was minus 15. The menses had been regular until 3 months before admission.

Ocular manifestations. Vision in each eye was 2/60. The fields showed practically a bitemporal hemianopsia, although vision was not wholly lost in the upper quadrant of each temporal field.

Right transfrontal craniotomy. December 20, 1926. The tumor presented prechiasmally but extended beneath and behind the chiasm. It contained straw colored fluid. A considerable portion of the cyst wall was removed and the wound closed.

Postoperative course. The patient recovered from the operation and 8 years later has no signs of recurrence (Fig. 41).

Histological report. The tumor was a typical stalk tumor, often styled adamantinoma. It was composed of the typical branching epithelial tree, with the basal ameloblastic layer, extensive stroma, cysts and calcium deposits in the thick fibrous capsule.

THE PATHOLOGY OF HYPOPHYSEAL STALK TUMOR

Of all the tumors included in this collective review the hypophyseal stalk tumor enjoys greater distinction than any other. Aneurisms, pseudotumors, fibroblastomas, and adenomas in this region can claim no distinctive features. The same cannot be said of the Rathke's cleft tumor and the hypophyseal stalk tumor. Hence we will discuss at greater length the pathological features of this group.

These tumors arise from the remains of the Rathke pouch. After the Rathke pouch has lost its connection with the buccal cavity there remains behind a so called duct composed of stratified epithelium representing the former connection with the buccal cavity. This duct has been called the "craniopharyngeal duct" but, as stated in my introductory remarks, erroneously so, and we have elected to designate it as the "hypophyseal stalk" and will refer to the tumors originating therefrom as "hypophyseal stalk" or simply as "stalk tumors."

The cells composing this duct may disappear completely or groups of them may be carried along with the anterior lobe of the hypophysis and be implanted along the superior surface of this lobe near the diaphragma sellæ or along the infundibulum at its union with the tuber cinereum at the base of the brain. The frequency with which these epithelial rests occur is shown in the investigation of Susman, who found 71 of 230 adult human hypophyses, or 30.4 per cent with epithelial rests. An even higher incidence is reported by Carmichael who found them in 39.1 per cent of adult hypophyses. The majority of these cell rests were epithelial in structure similar in histological structure to

the epithelial portions of the stalk tumors, and from them the stalk tumor has its origin.

These epithelial rests have a lower and upper location. From the lower group arise the tumors, which though primarily intrasellar may burst through the diaphragma sellæ early in their career and lie chiefly above the sella. In this lower group of tumors, the sella is enlarged often to a marked degree and the hypophysis compressed or completely destroyed. The sellar destruction is caused partly by the fact that the tumor is primarily intrasellar and grows first within the sellar boundaries and partly also by the suprasellar extension. This attains large dimensions and destroys the sellar walls by pressure.

Tumors arising from the upper group of cells, those just beneath the third ventricle, are entirely suprasellar. At times they grow into this ventricle and block the outlet of the lateral ventricle. If the tumor be large enough, the sella, and the hypophysis too, may be entirely destroyed.

Lying above the sella turcica as these tumors do, they encroach upon the chiasm and optic nerves. The chiasm is stretched over the tumor and often flattened out, so too the optic nerves if the tumor be of large dimensions.

The position of the tumor in relation to the optic chiasm is important. It may lie below the chiasm, the latter straddling the tumor, and present just in front of the chiasm. Or, lying behind the chiasm it may push the latter forward and make the tumor inaccessible.

These tumors vary a great deal in size; some are small, others very large. One of my tumors was a small lesion covering the floor of the third ventricle; another was so large that, projecting forward between both frontal lobes, it compressed the anterior and middle cerebral arteries and caused softening in their distribution. Many of these tumors are retrochiasmal; they grow backward rather than forward and occupy the base of the brain from the chiasmal region to the pons. Whether large or small, they are almost always so adherent to the structures at the base of the brain and to the hypothalamus that it is wellnigh impossible to enucleate them without serious injury to these important structures. The stalk tumors are discrete lesions well encapsulated, but because of their attachment to adjacent structures they must be looked upon as malignant rather than benign. This attachment is not due to invasion of the base of the brain by the tumor but to firm adhesions. The capsule of the tumor is adherent to the basilar structures at many points and so firmly attached that it is impossible with any degree of safety to separate the tumor from the adjacent structures.

Not only may these tumors grow forward into the anterior fossa but they not infrequently grow upward into the third ventricle. Thus arise signs of increased intracranial pressure and hypothalamic involvement.

The tumors in question are partly cystic and partly solid. The cystic portion varies greatly in size. In some tumors it may constitute three-fourths or seven-eighths of the tumor, in others it is much less extensive. Of the solid portion, much is often calcified or even ossified. In one case in my series the tumor was so extensively calcified that it was most difficult to obtain a piece for sectioning. Much of the solid portion is often necrotic. Usually these tumors have thick, firm, tough capsules so that even though the cyst be evacuated the cyst wall may not collapse.

The microscopic structure of these tumors is quite constant. They consist of a "solid epithelial tree with branching and anastomosing offshoots" (Fig. 42). They are composed of epithelial columns which intertwine and anastomose, forming a complicated and often confusing network of columns, among which is a more or less abundant stroma. The amount of the epithelial structure varies a good deal with different tumors; in some it is abundant, in others scarce and the caliber of the column varies from a very thin, cord-like structure to very plump epithelial growths.

The tumors are said to resemble the embryonic enamel organ, and typical sections from the epithelial tree show a basilar layer of columnar cells, a stratum intermedium and a stellate layer. Often, however, these three layers are not seen in the epithelial columns. Either the stratum intermedium is missing, or the stellate layer lacks the absolutely characteristic appearance that it possesses in the

Fig. 34. Case 9. Photograph of the patient at the age of 16 years. He had always been underdeveloped and was 3 years behind in his studies. He complained of headache and sleepiness most of the time; 1 year previously his vision began to fail. There were convolutional atrophy, a shadow of a calcified tumor and complete atrophy of the dorsum sellæ, and the floor of the sella was markedly depressed. There was bitemporal hemianopsia. Vision in the right eye was 6/60; in the left, 6/30. The pathological diagnosis was adamantinoma of the craniopharyngeal duct.

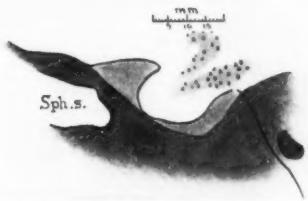


Fig. 35. Case 9. A sketch of the roentgenogram drawn to scale showing areas of calcification and enlargement of the sella turcica.

Fig. 36. Case 9. Photograph of hypophyseal stalk tumor extending from the frontal lobe to the pons.

enamel organ. The latter is a common observation. The basilar layer, spoken of as the layer of ameloblasts, has a well defined basement membrane, above which lie columnar cells with oval, elongated nuclei of a vesicular nature, and with poorly defined cytoplasm. Unlike the ameloblasts in the enamel organ, these cells are often not in a single layer but tend to assume a more or less stratified formation. The distinction between one cell and another in this layer is not sharp because the cytoplasm of one cell seems to blend imperceptibly with that of another. Above this ameloblastic layer there sometimes lies a layer, two or three cells thick, which is at right angles to the ameloblasts. These cells have properties similar to the ameloblasts, but they are often lacking in many of the epithelial columns. Above them lies the stellate layer, which forms the pulp, so to speak, of the epithelial columns. These cells, when typical, appear as stellate cells, which form an anastomosing, almost syncytical mass, looking very much like primitive mesenchyme. They are often not found in this true stellate arrangement; the center of the epithelial column may be composed of cells looking much more like the cells of the stratum interme-

Fig. 37. Case 11. Photograph of a girl 12 years of age with signs of intracranial pressure, atrophy of dorsum sella, headaches, vomiting, choked disc, arrest of growth, and adiposity.

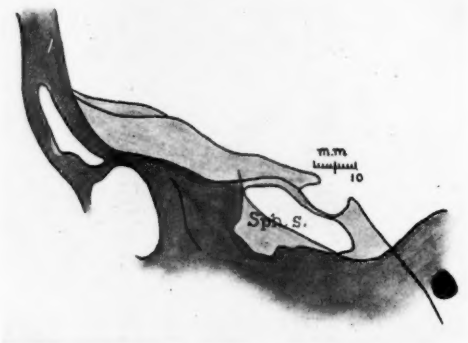


Fig. 38. Case 11. A sketch of the roentgenogram drawn to scale. Atrophy of dorsum sella, complete disappearance of posterior clinoid processes. No calcification.

dium. The nuclei in the cells of the stellate layer are vesicular and oval and cytoplasmic bridges are sometimes seen.

The stroma of these tumors varies in its abundance, in some plentiful and in others scanty. In some portions it has a distinctly fibrillar nature; in others it has a myxomatous appearance, and in still others it is almost completely degenerated. The number of cells within the stroma varies widely, but on the whole, cells are not very numerous within it. Many of the cells are of a fibroblastic nature. Often polynuclear cells are found within its meshes; large, vacuolated cells are often seen.

Evidences of degeneration constitute one of the most constant and interesting features of stalk tumors. Cysts are present in most of the tumors, sometimes in great abundance, in others in small numbers, but in some so cystic that they appear to be a conglomeration of cysts lying among epithelial columns. The cysts may be very small or may be so large as to fill almost an entire low power field; they are usually filled with a homogeneous, pink-staining, colloid-like material. Within the stellate layer are often large, swollen round cells with very small nuclei and with vacuolated cytoplasm. These cells probably represent cells of the stellate layer that have undergone hydropic degeneration.

In most of these stalk tumors, groups of stellate cells may be seen with hyaline degeneration; they are usually compressed, take a homogeneous pink stain and appear to be definitely degenerated. In some of them small granules of calcium are present, and it is possible that they may undergo calcification eventually. One of our tumors had a tremendous number of these areas. In a few tumors one could see the beginning of this degenerative process in the epithelial nests so often seen in the epithelial columns and it may be that these nests may eventually undergo degeneration of the sort described.

Calcification is seen in almost all the tumors and so abundantly that it may appear in every field (Fig. 43). The calcified areas may be seen as frequently in the stroma as in the epithelial columns, though probably more abundant in the former. It appears as small calcified granules, as a conglomeration of granules, as small flat sheets of calcified material, or as large irregular calcified masses. Bone formation is said to occur in some parts of the tumor, but we have not observed it in any tumor of our series.

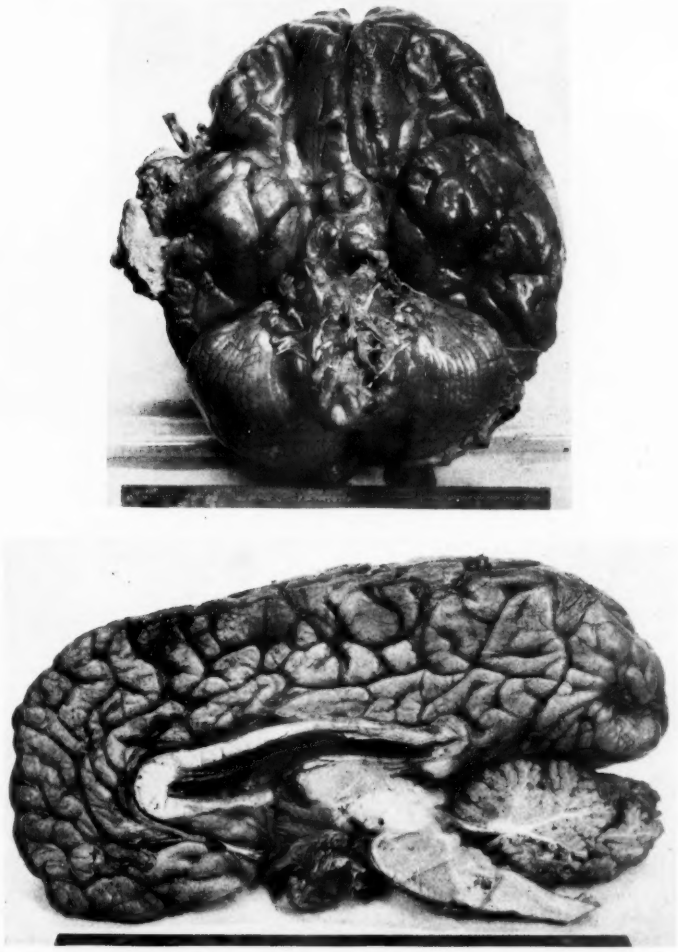


Fig. 39. Case 11. At autopsy a large tumor was found at the base of the brain with all the characteristics of a stalk tumor.

An important feature of the epithelial columns is the epithelial nests, composed of concentrically arranged cells in the columns. These are extremely abundant in some tumors and in others are a rather unimportant feature. Similar cell collections are sometimes found near the developing tooth in man though their significance is not clearly understood. Keratinization has been found in some of these cells, but Erdheim denied the presence of keratin granules.

Giant cells have been described in these tumors, but we have not seen them even in areas in which degeneration has been very active. Similarly, glial cells are said to be present in the stroma, but in a careful survey of our tumors we have failed to find any.

One interesting feature deserves further attention. The similarity of these stalk tumors or adamantinomas to the embryonic enamel organ has often been mentioned. In some instances the similarity is striking and in others

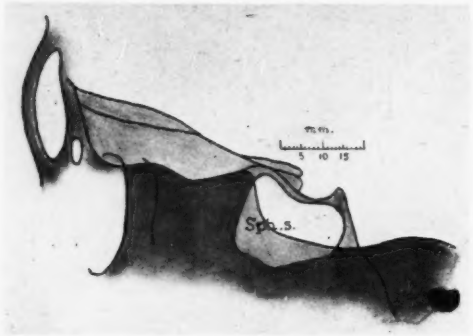


Fig. 40. Case 12. A sketch of the roentgenogram drawn to scale. No enlargement of sella turcica. No calcification.

much less so. In a general way they resemble the enamel organ, but it is strange that in none of the tumors described has enamel been found. The ameloblasts of the tumors contain no granules within their cytoplasm and the tumor itself possesses no structure that can be said to resemble enamel even remotely.

When discussing the origin of these tumors, we are confronted with a difficult problem. Presumably they arise from those remnants of the hypophyseal stalk that have been carried along the anterior lobe of the hypophysis in its evolution and development. In their structure the stalk tumors resemble adamantinomas and for this reason have been so called. But because the basilar layer of cells resembles the ameloblasts, it has been proposed by Ivy and Churchill that these tumors be called ameloblastomas. While it may be conceded that the hypophyseal stalk is composed of a stratified epithelium, no one has demonstrated that the type of epithelium in the stalk and the type seen in these tumors is identical. The stalk remnants are composed of stratified squamous epithelium; the epithelial portion of the stalk tumors, while epithelial in nature, is not squamous and has a structure quite distinctive. Certainly the ameloblast-like cells in the basilar layer are not to be found in the stalk remnants. Carmichael attempted to demonstrate the histological similarity of the stalk remnants and the stalk tumors, but a study of his sections fails to reveal a close resemblance. The tumor structures are epithelial in nature but not squamous in type.

Fig. 41. Case 12. Hypophyseal duct tumor. Photograph of patient 8 years after operation.

We have, therefore, the following situation: the hypophyseal duct in the embryo is lined with a low cuboidal epithelium, according to Carmichael, and with a "modified squamous epithelium" according to Duffy. The stalk remnants are composed of a stratified squamous epithelium of a special type unlike that of the stalk or its remnants. How can one explain the discrepancy and maintain the thesis that these tumors originate from the stalk? The paradox is not as difficult as it seems to appear.

The hypophyseal stalk in the embryo is intimately connected with the buccal cavity. Transition forms of epithelium are numerous in this region; transitions from ciliated columnar epithelium to low cuboidal or even flat cells and even to a modified squamous epithelium may be followed. It is not surprising, therefore, that the structure of the stalk tumors differs from that of the stalk or its remnants since they may represent only transition stages. It is more difficult to explain the great uniformity in structure of these tumors, for they are always alike, in their epithelial portions at least. Thus it is difficult to correlate them with tumors that arise from transitional epithelial elements. One would expect a diversity rather than a uniformity of structure. So, too, it is difficult to disregard the similarity which these stalk tumors bear to the primitive

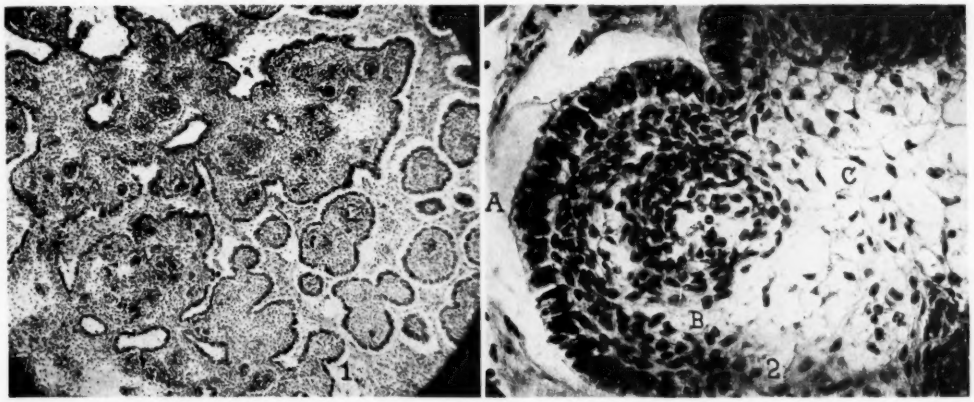


Fig. 42. Left, The epithelial tree which is characteristic of these tumors is clearly seen. Hematoxylin and eosin stain. Right, A high power view showing clearly a tooth bud with basilar layer of ameloblasts, *A*, the stratum intermedium, *B*, and the stellate layer, *C*. Hematoxylin and eosin stain.

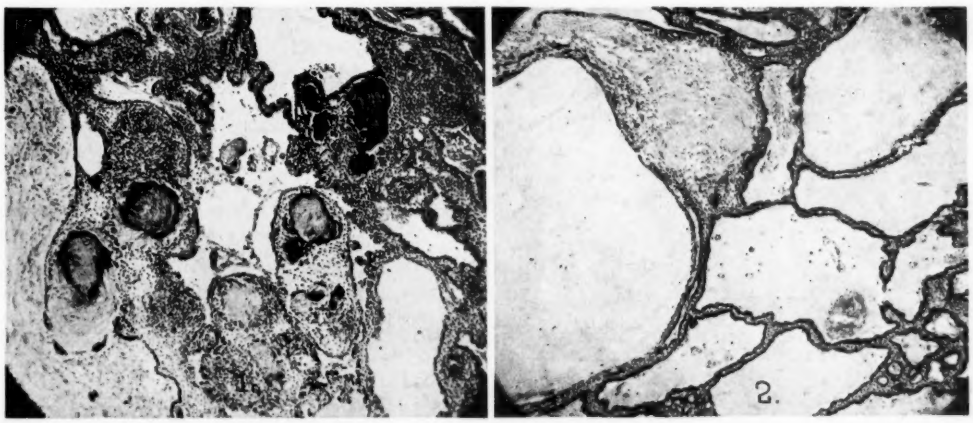


Fig. 43. Left, Calcium deposits are scattered about in the tumor tissue. Hematoxylin and eosin stain. Right, Here is seen the tendency of these tumors to form cysts. Hematoxylin and eosin stain.

enamel organ derived from the buccal epithelium. The basal layer of ameloblasts is present in them all and constitutes their outstanding characteristic. Furthermore, so called tooth buds may be found not infrequently in their midst. How one may correlate these discordant facts with the histological structure of the stalk and its remnants is not at all obvious. One can only assert that the connection of the stalk with the buccal cavity is so intimate that it is not surprising that epithelial structures derived from the mouth cavity are carried along with it in its migration.

Suprasellar teratomas. In a differential diagnosis of suprasellar tumor of congenital origin, one should keep in mind the suprasellar teratomas. These tumors, though rare, have been found in the region above the sella turcica, in the pineal recess, the third ventricle, rarely in the cerebellum, and in one of our cases, a metastatic tumor from the testis, a teratoma was found in the cerebral hemisphere. Their incidence among all tumors of the brain is about 0.5 per cent. Among 17 teratomas gathered from the literature by Hosoi, 2 were in the hypophyseal region; whereas among 23

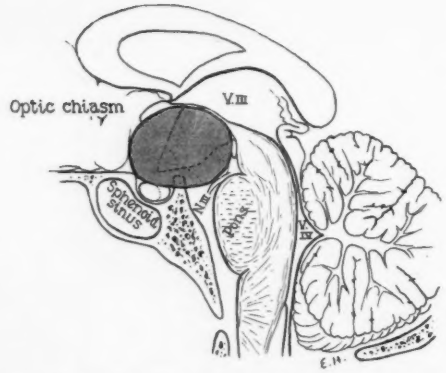


Fig. 44. Suprasellar teratoma eroding sella and compressing optic nerves and chiasm. It is chiefly retrochiasmal.

primary teratoid tumors, 8 were in the region of the hypophysis. Of 4 teratomas in my series, 2 were suprasellar, 1 was in the third ventricle, the fourth in the cerebral hemisphere. Both of the suprasellar teratomas occurred in young people, 1 a girl, the other a boy, both in their ninth year.

The relation of these congenital tumors to the structure around the sella differs somewhat from that of the more common stalk tumors (Fig. 44). They are chiefly retrochiasmal, displacing the optic chiasm upward and forward and sometimes compressing the optic tract. As a rule, the teratomas extend upward into the third ventricle, producing intense hydrocephalus and, by virtue of their size, may compress adjacent structures and give rise to such neighborhood symptoms. Sometimes the suprasellar portion may simply be an extension from an adjacent intracerebral teratoma.

They may be chiefly cystic or chiefly solid. The latter portion is usually firm, almost hard and may contain extensive calcified portions. In one of my cases the gross appearance of the tumor was that of a lipoma. In fact probably seven-eighths of the tumor was lipomatous. Only on microscopic examination were the derivatives of the other cell layers discovered and the tumor found to be a teratoma. Like the stalk tumors they are so firmly adherent to the structures at the base of the brain that complete extirpation is impossible. Like other congenital tumors of the brain, such as the stalk tumors, they occur not only in young but in older individuals, as in one of my patients who was in his fortieth year (File No. 28738).

Teratomas are usually large tumors, filling the entire interpeduncular space and encroaching upon the mesial aspects of both temporal lobes (Fig. 45). They may contain areas of calcification which are sufficient to cast an X-ray shadow. Histologically, they contain elements of all the germ layers and differ in no way from teratomas elsewhere (Fig. 46). Many tumors of this group, however, have been classified as teratoid tumors because they contain the derivatives of only some of the germinal layers. Typical teratomas in the brain, like those in the testis and elsewhere, contain epithelial elements, glands, bone, fat, blood vessels, cartilage, connective tissue, and muscle.

CASE 13. A child of 9 was under observation at intervals for 6 years. The lesion at first presented as a large cyst from which large quantities of an oily yellowish fluid were evacuated on two occasions in the first 2 years. Later the cyst was replaced by a calcified tumor which proved to be a teratoma. Convulsions, hemiparesis, homonymous hemianopsia, sexual precocity with headache, nausea and vomiting, were the outstanding symptoms. The patient died in his fifteenth year.

Clinical history. A boy, E. K., aged 9 years (File No. 65844), was first admitted to the neurosurgical service of the University Hospital June 1, 1921, with a chief complaint of convulsions. Two years before admission he developed severe headaches and spells of vomiting. Six months before admission his mouth was drawn to the right side, his gait was unsteady, and his memory began to fail. His head was increasing in size so that in 2 years the size of his hat changed from a No. 6 to a No. 7½. There was definite bulging of the right temporal region.

Examination revealed an underdeveloped boy with lower left facial paresis, adiadochocinesia and dysmetria left, impairment of pain and temperature sense on the left side of his body and face, a horizontal nystagmus on turning and past pointing. The discs were pale, the veins tortuous and there was a subsiding papilledema; left eye plus 4 diopters; right eye plus 5 diopters. The roentgenogram showed convolutional markings.

Operation. July 26, 1921. Exploratory craniotomy exposing the right motor and temporal cortex. The bulging of the temporal bone suggested an attempt at spontaneous decompression. From a cannula introduced into the right temporal lobe 170 cubic centimeters of a yellowish oily fluid escaped.

Fig. 45. Mixed tumor. Suprasellar.

The cyst was opened, the cavity was irregular in shape, and contained no tumor tissue. No attempt was made to remove the cyst wall and the wound was closed.

Readmission. February 13, 1923. In the interval, the patient's condition improved. The convulsions had ceased only to return July, 1922, and later the signs of intracranial pressure recurred. At this time the cyst was again evacuated and 500 cubic centimeters of the same yellowish oily fluid recovered.

At this time, when the boy was 11 years old, there were signs of sexual precocity (Fig. 47), the sex

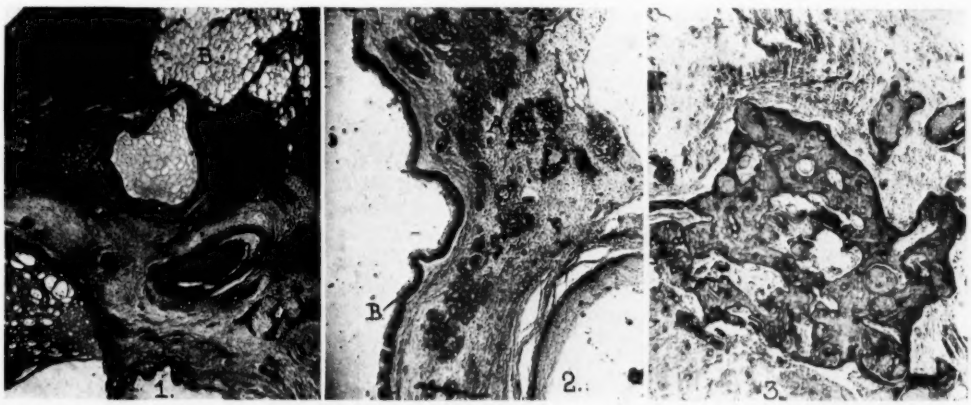


Fig. 46. Sections from the same tumor showing left, an area of cartilaginous tissue at *A*, fat tissue at *B*; center, an area of glandular tissue at *A* and epithelium at *B*; right, an area of osteoid tissue. Hematoxylin and eosin stain.

Fig. 47. Case 13. Suprasellar teratoma. Photograph of patient, left, taken beside boy of his own age, showing sexual precocity.

organs and pubic hair and his voice were comparable to those of an adult. He had grown 2 inches in 2 years. The nystagmoid movements, both horizontal and rotary, persisted. There was a definite hemiparesis and hemianesthesia. The patient walked with a spastic gait; dysmetria and past pointing were noted. He had developed at times a violent temper in which he attacked his mother.

Third admission. November 12, 1923. Since his discharge, February 21, 1923, he had been practically symptom free, was able to run about and play and had resumed his studies at school. An attempt was made to evacuate the cyst but only clear fluid was recovered, evidently from a distended ventricle.

Fourth admission. March 26, 1926, 5 years after the first admission, in the boy's fourteenth year. From November, 1923, he had remained free from convulsions and apparently in good health. January, 1926, his convulsive attacks returned. His nystagmus persisted and for the first time a left homonymous hemianopsia was observed. There were no motor or sensory phenomena, perhaps a slight adiadochocinesia in the left arm. Another attempt was made to evacuate the cyst but the exploratory cannula 4 centimeters below the surface came in contact with a firm gritty mass. No further exploration was made at this sitting. The roentgenogram taken after the operation revealed for the first time a large calcified shadow in the right hemisphere. The sella turcica measured 10 by 6 millimeters.

Fifth admission. August 23, 1927. There were no signs of intracranial pressure, but the convulsions persisted, though modified by luminal. The homonymous hemianopsia persisted, vision in each eye was 6/9. There were slight dysmetria, station unsteady, and a positive Romberg was recorded at this admission. Patient was discharged August 31, 1927.

Sixth admission. December 2, 1927. There were no striking changes in the patient's condition with certain exceptions. There was evidence of excessive sexual activity, his vision was 6/15 in each eye, there was a postpapillitic atrophy. For the first time the roentgenogram showed enlargement of the sella turcica and destruction of the dorsum sella. The basal metabolic rate was minus 20.

The record of this extraordinarily interesting case is recited because it serves for purposes of contrast between the stalk tumor and a teratoma. This case was under observation from 1921 to 1927, though we must add 2 years to the duration of the illness as the first symptom was observed 2 years before the patient came to the clinic. There are certain features of this case that find their counterpart in the records of our stalk tumors, notably these: the patient was a child in his ninth year, the tumor was cystic as are many of the stalk tumors, and, finally, though several years after the onset of the illness, the roentgenogram revealed areas of calcification. On the other hand there were other features in this case, chosen for contrast with the stalk tumors, which might have been interpreted as signs of differentiation. In this lad with a teratoma the outstanding symptom throughout his illness was convulsions. Again, the great majority of our stalk tumors had some evidence of hypophyseal dysfunction. Not only was there no evidence of such, but there was a syndrome of sexual precocity, which might direct one's attention to the pineal gland. Again, by way of contrast, the stalk tumor series in many instances suggested at least encroachment on the chiasm. The homonymous hemianopsia and the hemiplegia in this case of teratoma might well be accounted for by the presence in the right hemisphere of a lesion of considerable dimensions. Supplementary to these signs of diagnostic distinction, one might contrast the effect of the stalk tumors with that of the teratomas upon the optic nerves. In many of the stalk tumors, deterioration of vision to the point of

blindness was frequently recorded. Whereas in the teratoma patient, though afflicted for at least 8 years, his vision at the time of his death was 6/15 in each eye.

There are in the record of this instance of teratoma many other features that might arouse discussion not only as to diagnosis but as to treatment. But what has been said suffices to illustrate the essential differences in the physical expression of these two lesions, both as it were of congenital origin, the stalk tumor arising from a remnant of the hypophyseal stalk, the other, the teratoma, from some embryonic rest in the hypophyseal region. The origin of these tumors is by no means as clear as in the case of the stalk tumors but it is possible that the suprasellar teratomas arise from remnants of tissue connected with the buccal cavity.

(To be concluded.)

EVACUATION OF THE GALL BLADDER IN OLD AGE[1]

EDWARD A. BOYDEN, PH.D. (MED.SC.), AND SAM A. GRANTHAM, JR., M.D., MINNEAPOLIS, MINNESOTA

THE present article is the third of a series of statistical analyses utilizing the Graham-Cole method of visualizing the human gall bladder and dealing with the rate of emptying of the biliary vesicle in different periods of life.

In the first study (1928), the technique of computing volumes was refined, the various factors that might influence the rate of emptying were tested experimentally, and records were made of the entire period of evacuation of the gall bladder in 24 young men and women of medical school age. These observations established the main features of the curve of contraction in human beings and showed that the most important period is the first three-quarters of an hour after a test meal, by which time an average of two-thirds to three-quarters of the contents of the gall bladder has been evacuated, depending on the sex.[2]

In the second study (1934), after the data for young adults had been revised and 6 new cases added, observations were extended to 28 boys and girls, 6 to 11 years of age. This study revealed a striking difference between the mean rate of evacuation in the two groups, 80 per cent of bile being discharged in children as against 69 per cent in young adults, during the first 40 minutes after the test meal. When analyzed according to sex, however, this difference between children and adults was found to be due almost entirely to the faster emptying of the male, since the gall bladder of the girl seems to remain constant in its rate of discharge while passing from childhood to young womanhood.[3]

MATERIAL AND METHODS

The present study deals with the evacuation of the gall bladder in a group of 24 men and women between 60 and 78 years of age (average, 66 years). All of them were patients in the University Hospital who volunteered to submit to this test at no little inconvenience and discomfort to themselves.[4]

The procedure employed was similar to that used in the preceding studies. Having ascertained that the patient had a negative gastro-intestinal history, 3.5 grams of iodeikon was administered orally during the evening. The next morning, before breakfast, the patient was roentgenographed at 2, 4, 8, 12, 16, 20, 25, 30, 35, 40, and 45 minutes after drinking a glass of four egg-yolks mixed with an equal amount of milk and seasoned with sugar. Exact tracings of the cholecystograms were then made and the changing volumes of the gall bladder computed in cubic centimeters according to the methods described in the 1928 and 1934 articles. Subsequently, a contraction curve for each patient was obtained by plotting these volumes against time (Fig. 1). Finally, in order to secure a curve of the mean rate of emptying for each sex and for the whole group, the percentage loss of volume was calculated for each 8, 12, 20, 30, and 40 minute reading (Table I), and the reciprocals of the sums plotted against time. In this as in the previous study, the 2 minute reading has been considered as unity (unless otherwise noted), that being the earliest reading at which the slack in the gall-bladder wall is taken up by contraction.

[2]The test meal used in the first series was the original "Boyden meal" (1925) consisting of five egg-yolks well stirred in half a pint of cream. In the series dealing with children, the dosage was cut to three egg-yolks dissolved in milk and seasoned with sugar. In the more recent work the "meal" for adults has been standardized at four egg-yolks mixed with an equal amount of milk and seasoned with sugar. If it is necessary to disguise the egg taste, a little sherry flavoring or vanilla may be added. The essential ingredient of this "meal" is egg-yolk, no other natural food comparing with it as a means of emptying the gall bladder. (See discussion, p. 171, 1928 article.) This original observation has been verified by numerous investigators and particularly by Bronner (1928), an outstanding experimentalist in this field in Germany. Bronner uses egg-yolk alone, but the writer still favors the addition of milk or cream, partly to make the yolk more palatable.

[3]Since this article was written the writer has encountered three brief references to the emptying of the gall bladder in children. Weber (1927) seems to have been the first to consider the problem. While he was concerned chiefly with methods of visualization, his account contains two cholecystograms of an 8 year old boy that demonstrate evacuation of about half the contents of the gall bladder within 30 minutes after a "meal rich in fat." Bronner (1929) observed the rate of emptying in 10 cases, the youngest of which was 3 years old. Without giving any details, he states that he was able to demonstrate very extensive emptying in 1 to 1½ hours and that evacuation in children, as contrasted with that of old people, is characterized by the very reduced amount of bile left in the gall bladder an hour and a half after a meal of egg-yolk. Finally, Nemours-Auguste (1934) makes the statement, in his interesting book on the radiology of the biliary vesicle, that it takes less than an hour to empty the normal gall bladder of the child (p. 115).

[4]The authors are also indebted to Dr. O. H. Wangensteen, chief of the Surgical Service, and to Dr. L. G. Rigler, head of the Department of Radiology, for supplying hospital facilities for carrying on this work.

[1]From the departments of Anatomy and Surgery, The University of Minnesota; aided by a grant from the medical research funds of the Graduate School.

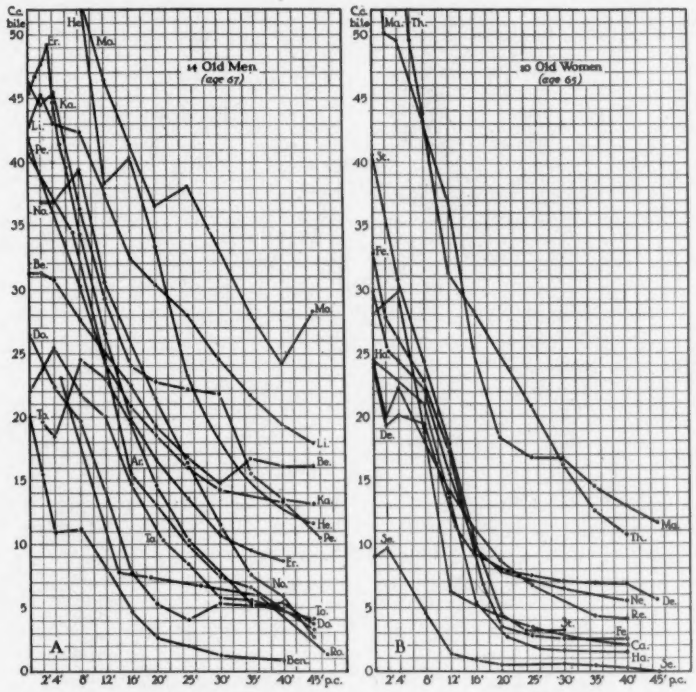


Fig. 1. Individual contraction curves of 24 *old* adults, covering the first phase of evacuation of the gall bladder. Ordinates, cubic centimeters of bile in fundus, body (and infundibulum) of gall bladder; abscissas, minutes post cibum (after a meal of four egg-yolks and milk); *Er.*, *He.*, *Mo.*, etc., names of patients. See corresponding abbreviations in first column of Table I for original data.

RATE OF EMPTYING IN SEVENTH DECADE

When the assembled contraction curves of old and young adults are compared (Figs. 1 and 2), no outstanding differences are apparent although it may be noted that the curves for the older group are somewhat steeper and more regular; also that larger gall bladders are more frequent there than in the younger group. The latter observation is in accord, perhaps, with Luetkens' statement that the biliary vesicle tends to become ptosed and overdistended in old age. Furthermore, the older women exhibit a rather surprising uniformity (Fig. 1 B), most of the curves of contraction tending to run closely parallel. A similar conservative tendency has been observed in young girls (see Fig. 7, ref. 3) but it has not been observed particularly in young women (Fig. 2 B).

These observations, however, are more or less incidental, the principal value of the graphs being to give some idea of the extent of individual variations. A true appraisal of the rate of emptying may be obtained only by examining the mean percentage loss of volume for the whole group. When this is plotted as a graph (Fig. 4 B, solid line), the curve for old people takes up a position intermediate between the curve for young adults and that for children (see also Fig. 3 A and B). In other words, the gall bladder of the seventh decade seems to be emptying faster than that of the third decade. Yet, when the data for the two groups are submitted to statistical analysis (Table II), it appears that the differences are doubtfully significant; for only in the 40 minute readings are the differences between the means equal to twice the standard error.

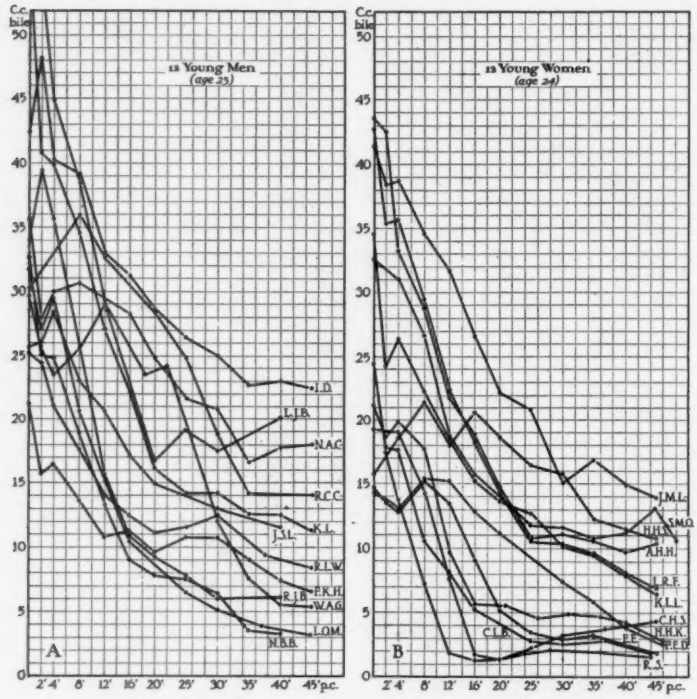


Fig. 2. Individual contraction curves of 24 *young* adults, covering the first phase of evacuation of the gall bladder, following a meal of five egg-yolks and cream (see footnote 1). For original data, see Table III, Boyden and Fuller, 1934. For mean rate of emptying according to sex, see Figure 5 B. For methods of computing volumes of gall bladder, see Boyden, 1928.

That is, the probability (P×100) that the differences might be due to random sampling is as great as 4.5 times in a hundred.[1]

Nevertheless, since the differences between the mean rate of emptying in old age and that in childhood are likewise without significance —even though the child gall bladder empties significantly faster than that of the young adult (1934 article)—it is necessary to consider the possibility that the motility of the adult gall bladder increases with age. If this be true, then it must be due either to progressive hypertrophy of the gall-bladder musculature, or to a lessening of resistance at the duodenal end of the common bile duct.

[1]In ordinary statistical parlance, if a difference occurs less than five times in a hundred it is assumed that it is not due to chance. The writers are greatly indebted to Dr. Edith Boyd for supervising the statistical analyses in this article.

What evidence exists, however, is conflicting. Thus Luetkens (1926) was unable to substantiate Charcot's claim that the gall-bladder musculature atrophies in old age. More often he received the opposite impression, namely of a slight hypertrophy of individual muscle fibers and so of the whole tunic. But he did note a sagging and distention of the lower end of the gall bladder in old age, which seemed to be associated with a weakening of the elastic fibers. Also, in some cases he observed atrophy of the mucosa and sclerosis of the blood vessels. On this basis Nemours-Auguste, 1934, assumes a lengthening of the time of evacuation in old age.

Nor have the authors found any evidence that suggests a progressive weakening of the duodenal or choledochal musculature. Accordingly, it seems less probable that the gall

TABLE I.—EMPTYING OF GALL BLADDER IN OLD ADULTS

A. 10 old women	Age	Weight pounds	Cause of hospitalization	Volume at intervals after eating									
				2 minutes * c.cm.	8 minutes		12 minutes		20 minutes		30 minutes		40 minutes	
					c.cm.	Per cent loss	c.cm.	Per cent loss	c.cm.	Per cent loss	c.cm.	Per cent loss	c.cm.	Per cent loss
Re.	67	118	Carcinoma, breast	19.8	18.0	9.28	13.9	30.00	8.6	57.00	5.4	75.87	4.2	79.04
Ca.	62	141	Carcinoma, breast	28.1 (0 min.)	18.7	33.33	6.3	77.50	4.2	85.19	3.0	89.74	2.1	92.60
Ne.	61	115	Carcinoma, mouth	24.4 (4 min.)	22.2	9.18	15.5	36.40	7.8	67.87	6.6	73.12	5.5	77.38
Ma.	60	103	Pernicious anemia	50.1	43.7	12.85	37.0	26.26	18.4	63.29	16.6	66.96	13.0	74.14
St.	78	148	Cataract	30.7 (4 min.)	24.3	20.80	17.8	42.19	4.5	85.42	3.2	89.58	5.9	89.58
Fe.	70	115	Lacerated pelvic floor	27.8	22.4	19.54	17.7	36.50	3.5	87.36	2.6	90.52	2.5	91.10
Th.	64	125	Carcinoma, cervix	56.1 (5 min.)	43.7	22.10	31.3	44.21	25.0	55.44	16.3	70.95	10.8	80.75
Se.	66	105	Hydronephrosis	9.0 (0 min.)	4.5	50.44	1.4	84.96	0.5	94.69	0.5	94.69	0.24	97.35
Ha.	55	125	Carcinoma, uterus	24.4 (0 min.)	21.1	13.45	13.6	44.26	3.8	84.26	1.7	93.12	1.5	93.77
Ro.	69	103	Lacrimal fistula	19.3	19.3	00.00	13.0	32.39	8.2	57.69	7.0	63.50	6.8	64.75
	†65.2	†119.8		†29.0		190.97		454.67		738.21		808.05		840.46
Mean percentage loss in 10 old women						19.10		45.47		73.82		80.8		84.05
B. 14 old men														
Ro.	61	150	Carcinoma, tongue	23.0 (5 min.)	18.0	21.60	11.2	51.22	7.2	68.64	6.6	74.29	4.4	80.84
Be.	70	135	Carcinoma, mouth	30.8 (4 min.)	27.7	10.00	25.0	18.70	19.2	37.66	14.8	51.95	16.0	51.95
Ka.	70	173	Carcinoma, lips	44.5	36.3	18.43	29.3	34.16	22.8	48.76	21.8	51.00	13.5	68.66
Ta.	69	159	Carcinoma, ear	22.0 (0 min.)	21.8	1.09	20.3	7.64	11.4	48.37	5.8	73.82	3.9	82.18
Mo.	73	159	Carcinoma, rectum	48.6 (0 min.)	(52.7)	0.00	46.3	4.74	36.6	24.69	33.0	32.10	24.1	50.41
He.	67	120	Pulmonary tuberculosis	45.5	(54.2)	0.00	37.4	17.89	33.3	26.86	17.8	68.88	12.6	72.30
Do.	72	109	Carcinoma, mouth	22.3 (4 min.)	19.7	11.83	14.0	37.28	5.3	76.35	4.1	81.72	4.1	81.72
Ar.	72	134	Trifacial neuralgia	34.4 (7 min.)	32.0	6.98	24.5	28.78	13.1	71.92	7.4	78.49	4.8	86.05
To.	61	164	Carcinoma, tongue	28.4 (4 min.)	(24.4)	0.00	(23.5)	0.00	14.5	21.20	7.7	58.16	4.7	74.46
Ben.	61	164	Carcinoma, esophagus	15.5	11.2	27.75	8.1	47.87	2.5	84.00	1.3	91.74	0.9	94.33
Li.	72	120	Chronic inflammation of forehead	42.9 (0 min.)	42.4	1.17	37.6	12.35	30.3	24.48	24.4	43.12	19.4	54.76
Pe.	60	137	Carcinoma, prostate	38.7	30.2	21.96	24.2	37.47	18.5	52.20	14.2	63.31	13.6	64.86
No.	63	146	Aortic insufficiency	36.9	39.5	0.00	30.6	17.14	21.4	42.08	11.5	68.76	5.9	83.95
Er.	63	171	Secondary anemia	44.7 (0 min.)	34.3	23.26	26.6	40.61	16.6	62.79	10.6	76.21	8.6	80.68
	†66.7	†145.7		†33.4		144.07		355.85		690.00		913.55		1027.15
Mean percentage loss in 14 old men						10.29		25.42		49.29		65.25		73.27
Mean percentage loss in 24 old adults						13.96		33.77		59.51		71.73		77.82

*Considered as 100 per cent; substitute readings are noted in parenthesis.
†Average.

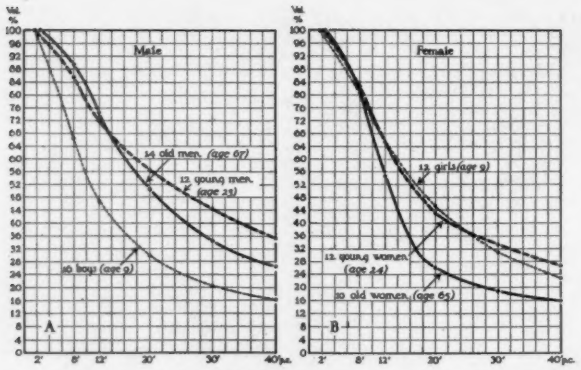


Fig. 3. Graphs illustrating the mean rate of evacuation of the gall bladder in childhood, early maturity and old age; arranged for comparison of age differences in the same sex. A, Male; B, female. Ordinates, percentage of bile in gall bladder, based on the two minute reading (see 5th column, Table I); abscissas, minutes post cibum.

bladder empties faster in old age than that our samples of the older population are not representative of the old age group. In other words, it is quite likely that the curve for old age shown in Figure 4 B represents the reaction of the more favored members of a hospital group—namely, those who have escaped infection or obstruction of the biliary tract. For when we examine the total number of patients subjected to these tests, it is apparent that more individuals in the old age group had to be eliminated on account of non-visualization of the gall bladder than in either of the other age groups (see last column, Table III). In the medical students, for instance, 100 per cent of all gall bladders tested by the Graham-Cole method were visualized; in the hospital children, at least 86 per cent could be seen; but in the oldest group only 74 per cent were visualized. Furthermore, in comparing the series that were discarded because of obliterating accumulations of gas and stools, one should bear in mind that the 8 children grouped in the third line and column of Table III are much less likely to have been pathological than the 5 old people in the fifth column, for it is well known that air is swallowed in much larger amounts by children than by adults.

A survey of the three groups thus leads to the conclusion that the medical student group is the most representative one, that the children come next and the old age group last. Accordingly it is believed that the most that can be concluded from the mean curve of emptying in the seventh decade is that if the biliary tract escapes pathological alteration its power of evacuation will not lessen with age.

Apparently, the only other investigator to subject the matter to experiment, has come to similar conclusions. Thus Bronner (1929) who investigated 6 patients between the age of 60 and 70 years—each with a negative stomach and gall-bladder history—found that up to the first 90 minutes after ingestion of egg-yolk the motility of these gall bladders seemed in no way to have been retarded. This convinced him that their musculature was in no way insufficient. On the other hand, he observed that there was a much greater residue of bile in the gall bladders of 6 older patients (90 minutes after egg-yolk) than in 10 young children whom he examined. He estimated that it ranged from 1/10 to 1/2 the ante-cibal volume—an average residue of 25 per cent—which is more than twice as much as the writer found in 24 young adults (see Table III, 1928). Although Bronner's cases were few in number and his estimates were merely guesses, it is possible that the later and least important places of contraction in old age undergo retardation or curtailment.

TABLE II.—STATISTICAL ANALYSES

Time interval, min.	Cases	Mean and standard error	Cases	Mean and standard error	Difference and standard error	Difference standard error	Probability integral
A. Old adults vs. Young adults							
8	24	13.96±2.585	24	15.75±3.134	−1.79±4.063	.441	0.660
12	24	33.77±4.125	24	31.33±4.839	+2.44±6.359	.384	0.704
20	24	59.51±4.513	24	50.08±5.566	+9.43±7.166	1.316	0.186
30	24	71.73±3.341	24	61.06±4.600	+10.67±5.685	1.877	0.060
40	24	77.82±2.701	24	68.87±3.530	+8.95±4.445	2.013	0.045
B. Old men vs. Old women							
8	14	10.29±2.782	10	19.10±4.505	−8.81±5.295	1.664	0.098
12	14	25.42±4.388	10	45.47±6.270	−20.05±7.653	2.620	0.009
20	14	49.29±5.601	10	73.82±4.738	−24.53±7.336	3.344	0.001
30	14	65.25±4.372	10	80.81±3.741	−15.56±5.704	2.704	0.007
40	14	73.37±3.626	10	84.05±3.282	−10.68±4.891	2.184	0.030
C. Adult men vs. Adult women							
8	26	12.12±2.157	22	18.08±3.514	−5.96±4.123	1.446	0.147
12	26	26.59±3.501	22	39.59±5.184	−13.00±6.255	2.078	0.038
20	26	46.62±4.562	22	64.46±5.114	−17.84±6.853	2.603	0.009
30	26	60.83±3.507	22	72.97±4.525	−12.14±5.725	2.121	0.034
40	26	69.30±3.024	22	78.13±3.284	−8.83±4.464	1.978	0.048

SEX DIFFERENCES IN RATE OF EMPTYING

The mean rate of evacuation in the three age groups according to sex is indicated in Figure 5. In the 1934 article, it was shown that the more rapid emptying of the biliary vesicle in boys than in girls (Fig. 5 A) was statistically significant. But it could not be demonstrated statistically that the gall bladder of young women emptied faster than that of young men. It was believed, however, that the consistent differences between the two curves (Fig. 5 B) indicated that larger samples would probably show a sex difference in favor of the female. Thus it was pointed out that 6 additional cases in men revealed a similar slowness of emptying.[1] Also it had been shown in the 1928 article that it took nearly twice as long to empty all but 3 cubic centimeters of the contents of the gall bladder in 12 young men as it did in 12 young women—namely, 128 as against 68 minutes (Table III).

We were not surprised, therefore, when statistical analysis of the curves for old age (Fig. 5 C) showed that the rate of emptying for the older women was significantly faster than that for the older men. For, as indicated in Table II B, the probability that such differences might be due to random sampling is less than 1:100 during the period when the gall bladder is emptying the fastest (12 to 30 minutes after meals). Similarly, when the data for young and old adults are combined, statistical analysis again decides in favor of the female (Table II C).

The evidence in these three studies, therefore, points to a sex difference in all periods of life. Before puberty, the male gall bladder empties much faster than the female; after puberty it slows down to a rate that is distinctly inferior to that of the female which has pursued a constant tempo from childhood to old age.

Two questions at once arise. What is the meaning of this change in the tempo of the male and how can this conservatism of the female gall bladder be reconciled with its greater susceptibility to biliary disease? We would approach the problem by suggesting

[1] As these earliest cases had been roentgenographed at 15 minute intervals, the data could not be fitted to that in the table, since the latter was based on shorter intervals.

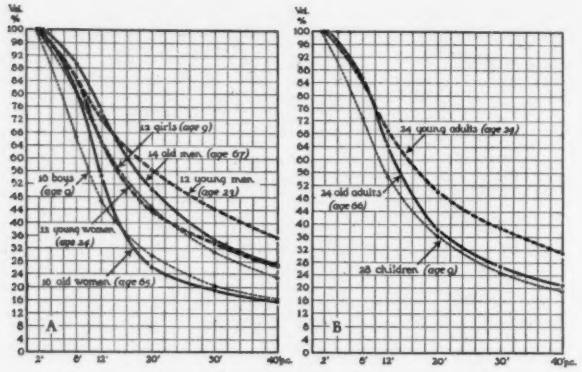

Vol. %
12 girls (age 9)
14 old men (age 67)
10 boys (age 9)
12 young men (age 23)
13 young women (age 24)
10 old women (age 65)
A
34 young adults (age 29)
24 old adults (age 66)
28 children (age 9)
B
2' 6' 12' 20' 30' 40'pc.

Fig. 4. Assembly drawings illustrating the mean rate of evacuation of the gall bladder. A, Six groups divided according to age and sex; B, three groups divided according to age alone.

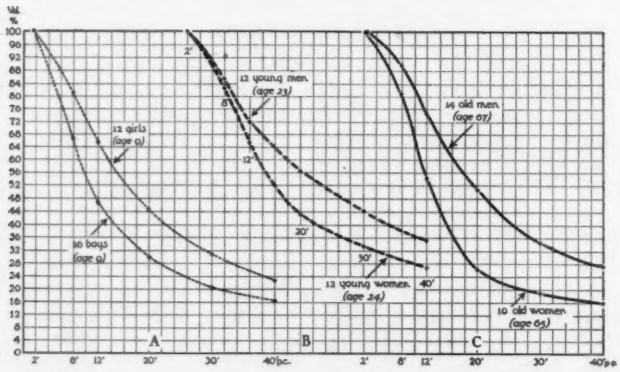


Fig. 5. The three age groups arranged for comparison of sex differences.

that the issue is not so much concerned with the gall bladder as with the intestinal tract; for the work of the last decade—particularly Ivy's notable demonstration of the existence of a duodenal hormone that specifically activates the gall-bladder musculature—makes it clear that, from the standpoint of motility, the human gall bladder is nothing but a puppet whose strings are being pulled by a chemical robot strategically placed in the upper half of the small intestine. It is believed, therefore, that sex differences in the rate of discharge of the gall bladder must be sought for in changes that occur during the prepubertal growth of the gastro-intestinal tract. It is not inconceivable, for instance, that the prime mover is the hypophysis and that the changes may be of the sort that Clark (1935) has recently described for the testis, in her demonstration of a prepubertal reversal of sex difference in the gonadotropic hormone content of the pituitary gland.

Similarly, the greater susceptibility of the female gall bladder to disease is now generally attributed to metabolic disturbances or to changes in the mucous membrane of the gall bladder following infection or obstruction of the duct system (cf. Ravdin, 1934), rather than to stasis caused by lack of motility of the gall bladder. Indeed, it appears that the human gall bladder is not even subject to inhibitory reflexes arising from painful stimulation of stomach and duodenum (Boyden and Rigler, 1934)—reflexes which in certain lab-

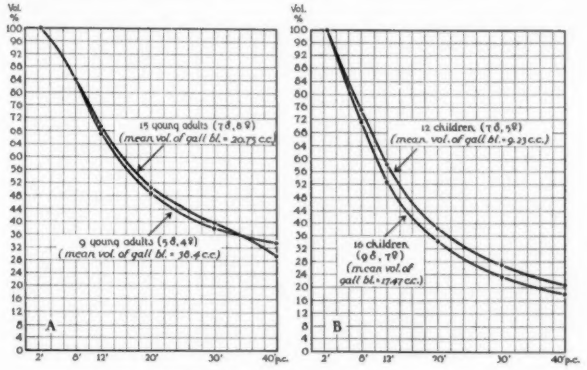

Vol. %
15 young adults (7♂, 8♀)
(mean vol. of gall bl. = 20.75 c.c.)
9 young adults (5♂, 4♀)
(mean vol. of gall bl. = 38.4 c.c.)
A
12 children (7♂, 5♀)
(mean vol. of gall bl. = 9.23 c.c.)
16 children
(9♂, 7♀)
(mean vol. of
gall bl. = 17.47 c.c.)
B
2' 5' 12' 20' 30' 40' p.c.

Fig. 6. Graphs illustrating the negative effect of size upon the rate of evacuation of the gall bladder. A, In young adults; B, in children.

oratory animals, retard the contraction of a gall bladder that is emptying after a meal of egg yolk (Oughterson and Mendillo, 1933; Birch and Boyden, 1930). Loss of motility in the human gall bladder is thus to be interpreted as a consequence and not as a cause of biliary tract disease.

THE EFFECT OF GALL-BLADDER SIZE ON THE RATE OF EMPTYING

Since it is assumed that in adults the female gall bladder is generally smaller than the male—and our data lend support to this view—it has seemed desirable to inquire whether the faster rate of emptying in the female is a function of its size. Accordingly, the data compiled from students of medical school age have been arranged in two categories—gall bladders having an initial volume of over 30 cubic centimeters and those having less.

When the mean curves of emptying for these two groups are compared (Fig. 6 A), the small gall bladders (having an average content of 20.75 cubic centimeters and a sex ratio of 47 per cent males) show approximately the same rate of contraction as the larger ones (averaging 38.4 cubic centimeters and having a sex ratio 55 per cent males). Obviously, in this group, size is not a significant factor.

Similarly, the children have been divided into two groups—those with gall bladders having an initial volume above 12 cubic centimeters (an average content of 17.47 cubic centimeters, with a sex ratio of 56 per cent males), and those below 12 cubic centimeters (averaging 9.23 cubic centimeters, and with a sex ratio of 58 per cent males). Here, also, there is no appreciable difference. If any-

TABLE III.—SUMMARY OF CASES IN THREE AGE GROUPS

	Young adults (students or younger members of laboratory staff)		Children (patients in University Hospital)		Old people (patients in University Hospital)	
	No.	Per cent	No.	Per cent	No.	Per cent
Number tested by dye	34		42		39	
Male	22	65	22	52	23	59
Female	12	35	20	48	16	41
Number well visualized	30*	94	28	67	24	62
Male	20	91	16	73	14	61
Female	12	100	12	60	10	63
Number insufficiently visualized for computation of volumes	2	6	8	19	5	13
Male	2	9	3	14	4	17
Female	..	..	5	25	1	6
Number not visualized	..	..	6†	14	10‡	26
Male	..	..	3	14	5	22
Female	..	..	3	15	5	31

Percentages are given in round numbers (hence, occasionally, they add up to 101 per cent).

*Two of these gall bladders (males) failed to empty after standard meal, therefore only 30 cases (88 per cent) could be used for plotting contraction curves. The first 6 males (Harvard series recorded in 1928 article) were omitted from the 1934 article, since those cholecystograms had been taken at only 15 minute intervals. Six new cases (Minnesota series) were substituted. The remaining 18 series were made at the University of Illinois.

†It is not known whether these cases were visualized, since the gall bladder region was completely obscured by gas or stools. The percentage of children with normal gall bladders ranges therefore from 86 per cent upward.

‡None of these cases was visualized, although the gall bladder region was not particularly obscured by gas. Only 74 per cent of old people were visualized, therefore.

thing, the smaller gall bladders empty slower, but not significantly so (Fig. 6 B).

Unfortunately, the old age group could not be separated successfully into two categories since in the group which exceeded 30 cubic centimeters in volume (an average of 42 cubic centimeters for 12 subjects), the males outnumbered the females 3 to 1. This was true also of the combined figures for young and old adults; for in gall bladders over 30 cubic centimeters (an average of 35.7 cubic centimeters for 21 adults) the males outnumbered the females 2 to 1. (Below the 30 cubic centimeters level an average of 20.9 cubic centimeters for 27 adults—the males constituted only 44 per cent.) The figures for children and young adults, however, afford no evidence that size is a factor in the rate of evacuation of the gall bladder.

CONCLUSIONS

This article presents a comparative study of the rate of emptying of the biliary vesicle in three periods of life: childhood, early maturity, and old age.

It is based upon cholecystographic examination of 115 individuals ranging from 6 to 78 years of age, 84 of whom were well enough visualized to permit computation of gall-bladder volumes at frequent intervals after a meal of egg-yolk.

Statistical analysis of this material indicates that the mean rate of evacuation of the gall bladder is faster in childhood than in early maturity, the difference being wholly due to the faster rate of emptying in boys.

After puberty the male gall bladder reverses its position, becoming significantly slower than the female.

Old adults in our series appear to evacuate the gall bladder faster than young adults, but in view of the fact that only 74 per cent of the gall bladders of older people could be visualized, as compared with 100 per cent of the young adults, it is believed that the old age group from which we obtained our figures represents a selected sample of the population —a group that has escaped biliary disturbances. Accordingly, these results are interpreted to mean that if the biliary tract escapes pathological alteration its motility does not become impaired by old age.

Old women have a much higher rate of emptying than old men—81 per cent of the contents of the female gall bladder being evacuated 30 minutes after a meal of egg-yolk, as compared with 65 per cent in the case of the male gall bladder.

These observations support the view that the greater susceptibility of women to gall-bladder disease is due to such factors as liver dysfunction, metabolic disturbances, impairment of the absorptive functions of the gall bladder, etc., rather than to any constitutional inferiority in the rate of evacuation of the biliary vesicle.

LITERATURE CITED

1. Birch, C. L., and Boyden, E. A. Reactions of gall bladder to stimulation of gastro-intestinal tract. II. Response to faradic excitation of stomach, small intestine and cæcum. Am. J. Physiol., 1930, 92: 301.
2. Boyden, E. A. Analysis of reaction of human gall bladder to food. Anat. Record, 1928, 40: 147.
3. Boyden, E. A., and Fuller, A. H. Anatomy and physiology of the gall bladder in children. Am. J Dis. Child., 1934, 48: 565.
4. Boyden, E. A., and Rigler, L. G. A cholecystographic and fluoroscopic study of reaction of human gall bladder to faradic stimulation of stomach and duodenum. Anat. Record, 1934, 59: 427.
5. Bronner, H. Studien zur Entleerung der Gallenblase (Cholecystographische Normaluntersuchungen). Beitr. z. klin. Chir., 1928, 142: 48.
6. Idem. Die cholecystographische Motilitaetspruefung der Gallenblase und ihre Ergebnisse (eine klinisch-roentgenologische Studie). Fortschr. a. d. Geb. d. Roentgenstrahlen, 1929, 39: 23.
7. Clark, H. M. A prepubertal reversal of the sex difference in the gonadotropic hormone content of the pituitary gland of rat. Anat. Record, 1935, 61: 175.
8. Ivy, A. C. The physiology of the gall bladder. Physiol. Rev., 1934, 14: 1.
9. Luetkens, U. Aufbau und Funktion der extrahepatischen Gallenwege mit besonderer Bezugnahme auf die primaeren Gallenwegsstauungen und die Gallensteinkrankheiten. Leipzig: Vogel, 1926.
10. Nemours-Auguste. Radiologie de la vésicule biliaire. Etude anatomique, fonctionelle et clinique. Paris: Masson et Cie., 1934.
11. Oughterson, A.W., and Mendillo, J. C. The effect of peritoneal irritation on the emptying time of the gall bladder and stomach. Surg., Gynec. & Obst., 1933, 56: 1013.
12. Ravdin, I. S. Biliary tract disease. J. Am. M. Ass., 1934, 103: 1504.
13. Weber, G. Cholecystographie bei Kindern. Monatschr. f. Kinderh., 1927, 36: 315.

CHOLECYSTITIS WITH CHOLELITHIASIS

A Clinicopathological Study of Sixty Patients

BÉLA HALPERT, M.D., and KNOWLES B. LAWRENCE, M.D., New Haven, Connecticut
From the Department of Pathology and the Department of Surgery, Yale University School of Medicine

THE purpose of this study was to reinvestigate the correlations between the clinical manifestations of cholecystitis and cholelithiasis, and the morphological changes in the gall bladder and its content. In order to attain this end the histories of 60 patients of the New Haven Hospital, known to have had gall-bladder disease, were surveyed and their gall bladders, obtained at operation, were studied. The data gathered thus far suggest that there is a relationship between certain types of biliary calculi and the morphological changes in the gall bladder; furthermore, that these changes are related to the clinical manifestations.

The cases studied were divided, for reasons which will become evident later, into three groups: (1) patients with "pure gall stones"; (2) patients with "mixed gall stones"; (3) patients with "combined gall stones."[1]

PATIENTS WITH PURE GALL STONES

Included in this group are patients whose gall bladders contained gall stones consisting entirely or mainly of one of the three stone-forming constituents of the bile: (a) cholesterol, (b) pigment calcium, (c) calcium carbonate. There were 8 of these: 7 (6 women, 1 man) whose gall bladders contained solitary pure cholesterol stones and 1 (a 32 year old man) with multiple pigment calcium stones (Table I). The mean age of these patients was 52.5 years. All the women had been pregnant one or more times. Recent acute attacks of upper abdominal pain lasting from a few days to several weeks were complained of by all the patients with pure cholesterol calculi. A history of definite, more or less severe, attacks prior to the acute phase was elicited from only 2 patients, both of whom had had these attacks for several years. The patient with pigment calcium stones complained of vague digestive symptoms for 4 to 5 years. Normal visualization of the gall bladders by the Graham-Cole method was obtained in one and impaired or no visualization in 5 patients. In 2 instances the non-opaque calculi were shown by contrast with the opaque medium filling the viscus.

Cholecystitis was observed in the gall bladders of all of the patients with pure gall stones (Table I). The chronic changes were slight and characterized by a small round cell infiltration in the tunica propria and the intermuscular connective tissue, the presence of occasional shallow Rokitansky-Aschoff sinuses, some hypertrophy of the muscular coat and a slight increase of the intermuscular and perimuscular connective tissues. These changes were noted in all 7 gall bladders which contained cholesterol stones. In 3 of these, in addition to the slight chronic change, there was a marked acute cholecystitis with edema, polymorphonuclear leucocytic infiltration and extensive hemorrhage and organization. In one of the gall bladders (P-1) the mucosa was thrown into plump folds and in the tunica propria of some of the folds large phagocytic cells containing lipoid substances were seen.

As mentioned before, 7 of the 8 gall bladders of this group contained pure cholesterol stones. All of these were solitary, oval, yellow white with a granular surface, measuring from 1.7 by 1.3 to 3.2 by 2.2 centimeters. Each had a radiating crystalline structure usually about a small center of black brown material. The radiopacity of the pure cholesterol calculi was slight. In the crevices of some of the crystalline structures, however, there were small amounts of pigment calcium and calcium carbonate which in roentgenograms visualized as radiating lines (Fig. 1). The pigment calcium stones present in the one remaining gall bladder were multiple dull black, irregular, crystalline structures 1 to 8 millimeters in diameter. They fragmented readily into small crystalline masses of calcium salts of bilirubin and bili-

[1]Halpert, Béla. New aspects of the formation and classification of gall stones. Arch. Path., 1928, 6: 623.

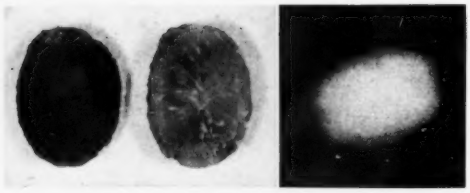


Fig. 1. Solitary cholesterol stone with radiating crystalline structure, from the gall bladder of a woman, aged 49 years (P-3).

verdin. They contained no cholesterol and no calcium carbonate. The radiopacity was moderate and homogeneous (Fig. 2). Calcium carbonate stones were not represented in this series.

PATIENTS WITH MIXED GALL STONES

Included in this group are patients whose gall bladders contained gall stones consisting mainly of two or of all three of the stone-forming constituents of the bile. The possible varieties of mixed gall stones are: stones consisting of cholesterol and pigment calcium (a+b), of cholesterol and calcium carbonate (a+c), of pigment calcium and calcium carbonate (b+c) and of cholesterol, pigment calcium and calcium carbonate (a+b+c).

There were 44 patients (34 women, 10 men) whose gall bladders contained mixed calculi (Table II). The mean age of these patients was 46.2 years. Most of the women were obese, the men well nourished. The majority of these patients complained of vague gastrointestinal symptoms for months or years. Some of them had recurrent attacks of acute pain, a few also had jaundice. Thirty of the 44 complained of recent acute abdominal pain. Normal visualization of the gall bladder was obtained in 2, impaired or no visualization in 20 of 22 patients examined by Graham-Cole method. Calculi were visualized in only 10.

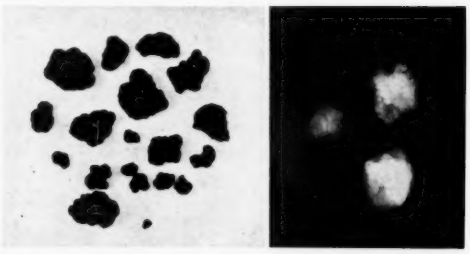


Fig. 2. Pigment calcium stones from the gall bladder of a man, aged 33 years (P-8).

The morphological changes in the gall bladders of the patients with mixed gall stones were: chronic cholecystitis in 29, and chronic cholecystitis with acute exacerbation in the 15 remaining. The chronic changes were characterized by the presence of hernia-like outpouchings of the mucosa, the Rokitansky-Aschoff sinuses, a hypertrophy of the muscular coat, an increase in the connective tissue of the tunica propria and the intermuscular and perimuscular connective tissues and a marked infiltration of all the connective tissue with small round cells. The hypertrophy of the muscular coat was manifested by an increase in size and perhaps also in the number of the individual smooth muscle cells and muscle bundles. Usually the muscular coat was thicker over the midportion of the body than over the fundus and neck of the viscus. Where hypertrophy of muscular coat was slight, the Rokitansky-Aschoff sinuses were shallow.

The gall bladders of the majority of the patients in this group, 38 of the 44, contained calculi composed mainly of cholesterol and pigment calcium. Admixtures of determinable amounts of calcium carbonate, calcium phosphate, and iron were also observed in some of these calculi. Usually the central portions contained more of the pigment calcium

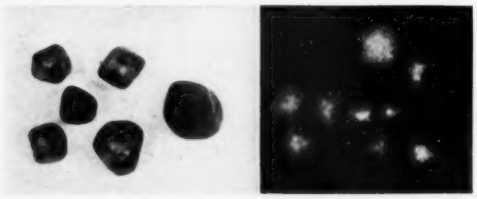


Fig. 3. Cholesterol and pigment calcium (a+b) stones from the gall bladder of a woman, aged 61 years (M-36).

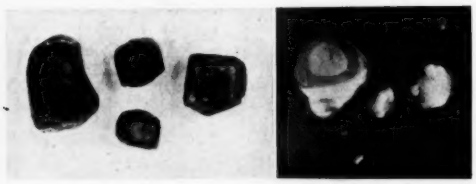


Fig. 4. Cholesterol and pigment calcium (a+b) stones from the gall bladder of a woman, aged 60 years (M-34).

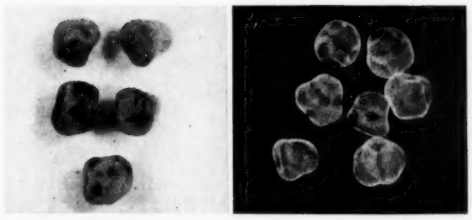


Fig. 5. Pigment calcium and calcium carbonate (b+c) stones from the gall bladder of a woman, aged 38 years (M-15).

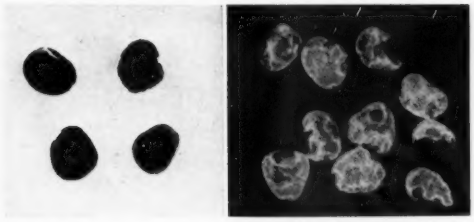


Fig. 6. Pigment calcium and calcium carbonate (b+c) stones from the gall bladder of a woman, aged 61 years (M-38).

than the peripheral (Fig. 3). The structure of the latter portion was amorphous or crystalline. The smallest stones were numerous and had the appearance of grains of sand. Some of these, and more particularly the larger ones, measuring up to 3 centimeters in diameter, were frequently faceted on one, two, or more surfaces. Their structure was layered or laminated with alternating rings of pigment calcium and cholesterol mixtures in varying proportions. Some of the adjacent faceted surfaces of the larger calculi seemed to "articulate" and the opposing surfaces appeared worn. In many of the medium sized and large calculi, central fissures were noted (Fig. 4). In 5 of the 38 gall bladders, the gall stones, though of similar chemical composition, had a different architecture. About single or multiple centers of pigment calcium with little cholesterol, a mass of amorphous cholesterol with little pigment calcium was seen. The surfaces of these calculi were roughly granular, light grey or white. They were soft and broke easily.

The roentgenograms of all the cholesterol pigment calcium stones revealed clearly the absolute and relative distribution of the slightly radio-opaque cholesterol and the moderately radio-opaque pigment calcium.

Mixed gall stones composed mainly of cholesterol and calcium carbonate (a+c) were not represented in this series.

The gall bladders of 3 patients contained calculi composed almost entirely of pigment calcium and calcium carbonate (b+c) with little if any cholesterol (Figs. 5 to 7). They were multiple, round or oval, dark brown or black, very firm, cutting with considerable resistance. The surfaces of one set of these stones had a "moth-eaten" appearance (Fig. 6). As expected the radio-opacity of the pigment calcium-calcium carbonate stones was more marked than any of the other mixed calculi.

The gall bladders of the 3 remaining patients of the group contained calculi composed of relatively great amounts of all three of the stone forming constituents of the bile. These cholesterol-pigment calcium-calcium carbonate stones (a+b+c) were also multiple and measured from 4 to 16 millimeters in diameter. Their surfaces were smooth or faceted (Fig. 8). The distribution of the various stone-forming components varied in the different stones or sets of stones. No definite laminations or radiations were noted. The radio-opacity was dependent on the relative

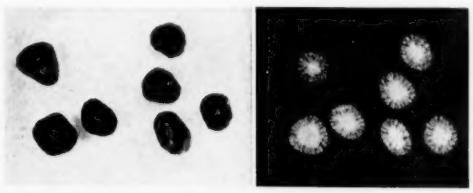


Fig. 7. Pigment calcium and calcium carbonate (b+c) stones from the gall bladder of a woman, aged 70 years (M-41).

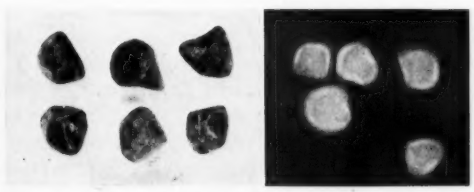


Fig. 8. Cholesterol, pigment calcium, and calcium carbonate (a+b+c) stones from the gall bladder of a man, aged 53 years (M-29).

TABLE I.—PATIENTS WITH PURE GALL STONES

Patient			Pregnancies	Duration of symptoms			Visualization (Graham-Cole)	Cholecystitis
No.	Age	Sex		Vague	Recurrent attacks	Recent acute attack		
1. Cholesterol (a) stones								
P-1 (11,017)	39	F	4	2 mos.		2 mos.	Normal	Chronic, slight
P-2 (11,247)	42	F	4	2 wks.		2 wks.	Impaired	Chronic, slight; acute, marked with organization
P-3 (9,327)	49	F	1			3 wks.	None	Chronic, slight; acute, marked with organization
P-4 (9,282)	52	F	1		4–5 yrs.	1 wk.	None	Chronic, slight; acute, marked with organization
P-5 (9,739)	64	F	2	years	1 year	1 wk.		Chronic and acute
P-6 (10,027)	67	M		1 mo.		1 mo.	Impaired	Chronic, slight
P-7 (11,342)	75	F	1			3 days		Chronic and acute
2. Pigment calcium (b) stones								
P-8 (10,667)	32	M		4 yrs.			Impaired	Acute, slight
3. Calcium carbonate (c) stones								

proportion of the more or less opaque components.

PATIENTS WITH COMBINED GALL STONES

Included in this group were patients whose gall bladders contained gall stones which had a nucleus of a pure gall stone and a shell composed of any one, or all, of the stone-forming constituents of the bile. There were 8 patients in this group, all women (Table III). The mean age of these patients was 53.2 years. Five patients were obese, the rest well nourished. Two had never been pregnant, the others from 2 to 12 times. Most of these patients complained of vague gastro-intestinal symptoms for several years. Four had had recurrent attacks of pain but none shortly prior to operation. The 4 others complained of recent, acute symptoms of a few days or weeks duration. Roentgenographic visualization of the gall bladder was impaired in all 4 patients examined. Calculi were visualized in 3.

The gall bladders of all of the 8 patients with combined gall stones showed chronic changes characterized by the presence of Rokitansky-Aschoff sinuses, hypertrophy of the muscular coat, an increase of the intermuscular and perimuscular connective tissues and a small round cell infiltration of all the connective tissue. In 4 of the 8 gall bladders, there was an acute exacerbation of the inflammatory process.

The gall bladders of 4 of the 8 patients in this group contained solitary combined stones which had a nucleus of a pure cholesterol stone with a crystalline radiating structure and a shell composed of layers of varying amounts of cholesterol, pigment calcium, and calcium carbonate. These stones were oval or round measuring from 2.5 by 2.2 to 4 by 3.2 centimeters. Their surfaces were finely or roughly granular. Roentgenograms of these calculi revealed little structural detail on account of their size and richness in markedly radio-opaque components (Figs. 9 and 10).

The gall bladders of the 4 remaining patients contained in addition to one large combined stone, one or more smaller mixed stones. The chemical composition and the architecture of the latter was the same as that of the shell of the large combined stone. This was evident on the cut surfaces as well as on roentgenograms (Figs. 11 and 12).

DEDUCTIONS

Gall stones of similar chemical composition and architecture are perhaps produced by disorders of the same kind and are likely to pre-

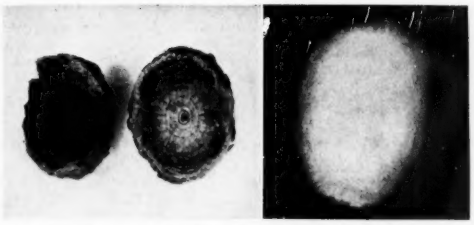


Fig. 9. Combined gall stone from the gall bladder of a woman, aged 61 years (C-6). About a cholesterol nucleus alternating layers of pigment calcium and cholesterol are desposited.

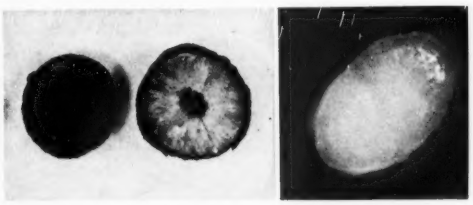


Fig. 10. Combined gall stone from the gall bladder of a woman, aged 72 years (C-8). A cholesterol stone with radiating crystalline structure forms the nucleus and layers of pigment calcium and cholesterol the shell.

sent the same set of clinical manifestations. This line of thought suggested that for the purpose of analysis, those patients whose biliary disorders resulted in the formation of gall stones of identical type, should be grouped together.

The 60 cases in this study were not selected and therefore comprise a random sample of patients with gall-bladder disease. There were 8 patients with pure, 44 with mixed, and 8 with combined gall stones.

In the patients with pure gall stones the clinical manifestations of gall-bladder disease were rather recent and the morphological changes in the gall bladder were either acute, or acute superimposed upon a slight or moderate degree of chronic change. These facts suggest that in this group of patients the cholecystitis followed rather than preceded the stone formation.

Most of the patients with mixed gall stones had recurrent attacks of acute abdominal pain. The prevalent morphological change in the gall bladders of this group was chronic cholecystitis. This was usually characterized by the presence of Rokitansky-Aschoff sinuses, hypertrophy of the muscular coat, and an increase in the connective tissue of the tunica propria and the intermuscular and perimuscular connective tissues, all of which showed a small round cell infiltration. Superimposed upon these chronic changes, there was in many instances an acute inflammatory process. The composition, structure, and size of the calculi in each gall bladder showed marks of the successive changes of their evolution. All of this suggests a causal relation between the chronic cholecystitis with recurring acute exacerbations and the formation of mixed gall stones.

In patients with combined gall stones the clinical manifestations as well as the morphological changes in the gall bladder were quite similar to those observed in patients with mixed gall stones. Combined gall stones, although older and usually larger, rarely caused more severe clinical manifestations than mixed gall stones of smaller size. The nucleus of a combined stone is, of course, older than its shell and therefore it seems reasonable to assume that the process which led to the for-

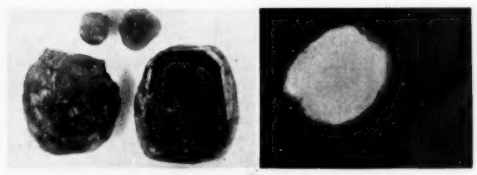


Fig. 11. One combined and several mixed calculi from the gall bladder of a woman, aged 71 years (C-7). The nucleus of the large stone is of pigment calcium and calcium carbonate (b+c) with a shell of cholesterol and pigment calcium.

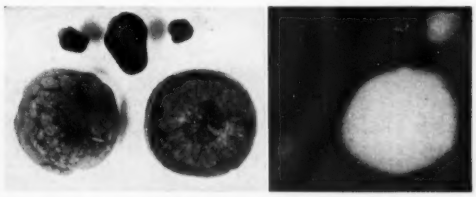


Fig. 12. One combined and several mixed calculi from the gall bladder of a woman, aged 45 years (C-3). The nucleus of the combined stone is of cholesterol, the shell is of pigment calcium and calcium carbonate rich in cholesterol (a+b+c). The structure and composition of the mixed calculi are identical with those of the shell of the combined stone.

TABLE II.—PATIENTS WITH MIXED GALL STONES

Patient			Pregnancies	Duration of symptoms			Visualization (Graham-Cole)	Cholecystitis
No.	Age	Sex		Vague	Recurrent attacks	Recent acute attack		
1. Cholesterol and pigment calcium (a+b) stones								
M-1 (10,105)	23	F	0		6 mos.	1 wk.		Chronic with slight acute exacerbation
M-2 (9,976)	24	F	3		6 mos.		None	Chronic
M-3 (9,217)	25	F	3			1 wk.		Chronic with acute exacerbation
M-4 (10,470)	26	F	3	18 mos.	18 mos.		Impaired	Chronic
M-5 (10,135)	26	F	0			2 wks.		Chronic
M-6 (9,795)	26	F	5		1 yr.	2 wks.		Chronic
M-7 (9,415)	27	F	3		3½ yrs.	2 days		Chronic
M-8 (9,928)	28	F	5	3½ yrs.	3½ yrs.	days		Chronic with acute exacerbation
M-9 (9,347)	30	F	1	2 yrs.	2 yrs.	days	Normal	Chronic, slight
M-10 (10,302)	32	F	1		11 mos.		None	Chronic, slight
M-11 (10,195)	34	F	3	years				Chronic
M-12 (G3812)	35	F	2		2 yrs.	weeks	Impaired	Chronic
M-13 (9,088)	35	F	4	years	3 mos.	days	None	Chronic, marked
M-14 (10,572)	38	M		years		4 days		Chronic
M-16 (10,831)	38	F	8	1 yr.		3 days		Chronic with acute exacerbation
M-17 (10,659)	38	F	4		1½ yrs.		Impaired	Chronic
M-18 (9,810)	41	F	0	years	4 yrs.	1 day	None	Chronic with acute exacerbation
M-19 (11,071)	43	F	2	4 mos.	4 yrs.		Impaired	Chronic
M-20 (10,965)	45	M		years		2 mos.		Chronic, slight
M-21 (10,069)	46	F	3		years			Chronic, marked
M-22 (10,402)	48	F	15	years	1 yr.	days	None	Chronic with acute exacerbation
M-23 (9,722)	48	F	2	4 mos.	4 mos.		Impaired	Chronic, marked
M-24 (9,228)	49	F	3	3 yrs.	years			Chronic, marked
M-25 (10,187)	49	F	0	30 yrs.	years	weeks		Chronic, marked, with slight acute exacerbation
M-27 (9,796)	52	F	3	12 yrs.		2 mos.	Normal	Chronic, slight
M-28 (10,678)	53	M		2 yrs.	2 yrs.	days		Chronic with acute exacerbation
M-30 (9,829)	53	M		9 yrs.		3 days		Chronic with acute exacerbation
M-31 (10,865)	53	F	15	2 mos.		2 days	None	Chronic with slight acute exacerbation
M-32 (10,394)	56	F	2	5 yrs.	5 yrs.	6 wks.	Impaired	Chronic
M-33 (9,167)	57	M		4 yrs.	4 yrs.	weeks		Chronic
M-34 (10,823)	60	F	3	25 yrs.	25 yrs.	11 days	None	Chronic with acute exacerbation subsiding
M-35 (10,210)	60	F	0	weeks		days		Chronic
M-36 (9,992)	60	M		25 yrs.	years		None	Chronic
M-37 (10,600)	61	F	7	years	years		Impaired	Chronic, marked
M-39 (11,090)	63	M		years		1 day		Chronic with acute exacerbation
M-40 (9,901)	65	F	8	40 yrs.	40 yrs.		Impaired	Chronic, marked
M-42 (10,610)	71	F	10	years	years	days	Impaired	Chronic
M-43 (10,104)	72	M		years	2 yrs.	days		Chronic with acute exacerbation
2. Cholesterol and calcium carbonate (a+c) stones								

TABLE II.—PATIENTS WITH MIXED GALL STONES—Continued

Patient			Pregnancies	Duration of symptoms			Visualization (Graham-Cole)	Cholecystitis
No.	Age	Sex		Vague	Recurrent attacks	Recent acute attack		
3. Pigment calcium and calcium carbonate (b+c) stones								
M-15 (10,425)	38	F	5			1 mo.	Impaired	Chronic
M-38 (11,395)	61	F	2	years	15 yrs.		None	Chronic, slight
M-41 (10,905)	70	F	2		1 yr.			Chronic
4. Cholesterol, pigment calcium and calcium carbonate (a+b+c) stones								
M-26 (10,693)	50	F	2	years	10 yrs.	weeks		Chronic
M-29 (10,731)	53	M		mo.		days	Impaired	Chronic with acute exacerbation
M-44 (9,461)	73	M			1½ yrs.	days		Chronic with acute exacerbation

TABLE III.—PATIENTS WITH COMBINED GALL STONES

Patient			Pregnancies	Duration of symptoms			Visualization (Graham-Cole)	Cholecystitis
No.	Age	Sex		Vague	Recurrent attacks	Recent acute attack		
C-1 (10,249)	40	F	0	2 yrs.	3 yrs.		Impaired	Chronic
C-2 (10,259)	44	F	7	4 yrs.	4 yrs.	weeks	Impaired	Chronic with acute exacerbation
C-3 (10,794)	45	F	4	6 mos.	6 mos.			Chronic
C-4 (10,841)	47	F	8	5 yrs.		2 days		Chronic with acute exacerbation
C-5 (10,146)	56	F	0		3 mos.			Chronic with acute exacerbation
C-6 (9,373)	61	F	5	years		weeks	Impaired	Chronic
C-7 (9,114)	61	F	2		5 yrs.			Chronic
C-8 (9,106)	72	F	12	years		2 days	Impaired	Chronic with acute exacerbation

mation of the nucleus preceded that which formed the shell.

SUMMARY

An attempt was made to correlate the clinical manifestation of cholecystitis and cholelithiasis with the morphological changes in the gall bladder and its content. Those patients whose biliary disorders resulted in the formation of gall stones of similar type were grouped together.

In the patients with pure gall stones, the clinical manifestations of gall-bladder disease were rather recent and the morphological changes in the gall bladder were either acute, or acute superimposed upon a slight or moderate degree of chronic change. It was, therefore, assumed that in this group of patients the cholecystitis followed rather than preceded the stone formation.

In the patients with mixed gall stones, the clinical manifestations of gall-bladder disease were of a chronic nature with recurrent acute attacks. The gall bladders of this group showed evidences of chronic cholecystitis and in many instances a superimposed acute inflammatory process. It was, therefore, assumed that a causal relation existed between the chronic cholecystitis with recurring acute exacerbations and the formation of mixed gall stones.

In the patients with combined gall stones, the clinical manifestations as well as the morphological changes in the gall bladders were quite similar to those observed in patients with mixed gall stones.

LIFE EXPECTANCY IN BILIARY-INTESTINAL ANASTOMOSIS

E. L. ELIASON, M.D., F.A.C.S., AND JULIAN JOHNSON, M.D., PHILADELPHIA, PENNSYLVANIA
From Service C of the Surgical Clinic of the Hospital of the University of Pennsylvania

ONE of the occasions upon which the surgeon is called to exercise his most astute judgment is when presented with an obstruction of the common duct that can not be removed with reasonable safety to the patient. If the gall bladder is present and the cystic duct is open, a cholecystogastrostomy or cholecystoduodenostomy offers an escape from a difficult situation. In other instances, the common duct or even the hepatic duct must be used for the anastomosis. The surgical textbooks and operative manuals merely mention these operations, or describe the technique, giving nothing as to the results. The recent surgical systems (35, 72) warn against the danger of ascending liver infection and imply that the life expectancy is short.

The first cholecystenterostomy was reported by Winiwarter in 1882. In 1894, Michaux reported a cholecystoduodenostomy done by Ricard. The patient died 53 days later with cholangitis. In the same year, Dujardin and Beaumetz reported a case of Charcot's intermittent hepatic fever following cholecystoduodenostomy. Since these original observations, there have been many reports of different types of operations for anastomosis of the biliary and gastro-intestinal tract, and many opinions expressed as to the presence or absence of cholangitis as a serious complication.

EXPERIMENTAL RESULTS

From the experimental standpoint, cholangitis with ascending liver infection seems to be an almost constant finding following biliary-intestinal anastomosis in dogs (24, 30, 40). Marinelli, however, reports that cholecystogastrostomy produces less liver infection than cholecystoduodenostomy. It has been pointed out that the gall bladder of the dog has accessory ducts which would increase the tendency to ascending liver infection. It is interesting to note that one monkey sacrificed 8 months after cholecystogastrostomy presented no liver infection (70). On the other hand, Gage, working in New Orleans, reported liver infection in 100 per cent of normal dogs, and that only 46 per cent of his dogs sacrificed 15 days after cholecystoduodenostomy had more liver infection than normal. Recently, Gentile published the results of experiments in dogs from which he concluded that ascending liver infection is not a danger after cholecystogastrostomy. Reasoning that the nature of a dog's food and habits made previous experiments not applicable to man, he divided the stomach, making a blind pouch of the distal end and connecting the proximal end to the jejunum. At a second operation, the gall bladder was anastomosed to the gastric pouch which was now separate from the current of food. He felt that such an arrangement more nearly approached bacteriologically what one finds in the human. The dogs were sacrificed 40 to 97 days after the second operation. He found no greater liver infection than before the cholecystogastrostomy was performed. These experiments are subject to the objection that there is no opportunity for reflux of food into the gall bladder such as does occur in the human (7, 8, 65).

TYPES OF OPERATIONS

It is generally agreed that the position of the anastomosis should by choice be in the stomach or duodenum rather than lower in the gastro-intestinal tract because there is less danger of ascending biliary infection. There seems to be little choice between the stomach and duodenum. The latter is preferred by many, because it more nearly simulates the normal. Experience has definitely shown, however, that cholecystogastrostomy is well tolerated (31). Many prefer it as they feel that it is a safer operation and liver infection is less likely than with cholecystoduodenostomy. Alexandroff, from cases collected from the literature between 1880 and 1918, compiled the figures shown in Table I.

TABLE I

Anastomosis of gall bladder to—	Cases	Mortality
Stomach	102	13
Duodenum	102	18
Small Intestine	257	34
Large Intestine	29	49

Most surgeons prefer to use the gall bladder for the anastomosis when it is accessible. Finsterer, however, removes the gall bladder to prevent further stone formation and does a choledochoduodenostomy. In support of such an operation is the fact that stones have formed in the gall bladder after cholecystoduodenostomy and caused obstruction of the anastomosis with resultant jaundice (53). In cases of deep jaundice, Walters (67) suggests performing the operation in two stages. We have found this of value.

Many methods of anastomosis have been suggested. Some do a simple lateral anastomosis (65), others use a button (52) or a rubber (16, 51) or metal (59, 61) tube. Roeder (60) suggested performing a plastic operation on the gall bladder to form a tube which is carried through the walls of the stomach to produce a valve-like action. However, he reported 2 patients who died with liver abscesses after this type of operation. Mason (44) also suggested an operation with this in view, but later, with Baker (45) reported a death with multiple liver abscesses after his operation. We have used a permanent tube in the gall bladder as described by Muller. However, cases have been reported in which the tube has become obstructed by deposits of bile salts (33). Finsterer emphasizes the importance of a wide opening and at the same time denies that the operation increases the danger of ascending infection. It seems likely that cholangitis would be best tolerated in the presence of a wide opening with adequate drainage.

A few successful indirect anastomoses have been performed, but these operations are still more or less curiosities. Such operations are, of course, done only as a last resort and carry a high percentage of failure. Jenckel reported the first indirect hepaticoduodenotomy when his patient was still well 4 years after operation. Odermatt recorded a case with death from cholangitis 6 years after a similar operation. Williams and Smithwick reported a patient well 16 years after the transplantation of a fistulous tract into the duodenum. Lahey has 2 cases of a similar nature well 7 and 8 years after operation. A complete monograph of the various types of operations on the biliary ducts has been published by Horgan.

INDICATIONS FOR OPERATION

The average surgeon has done a biliary intestinal anastomosis only when he has been forced into it. The indication is usually a common duct obstruction from carcinoma of the pancreas or bile ducts, chronic pancreatitis, stricture or traumatic injury of the ducts or a stone in the common duct that cannot be removed. Since Babcock's publications in 1920, a number of surgeons, especially in Europe, have performed cholecystogastrostomy for peptic ulcer. To this list of indications, Du Bose has added perforated gall bladder, acute pancreatitis, chronic obscure jaundice, perforated peptic ulcer, and marginal ulcer following gastrojejunostomy. Bérard and Mallet-Guy have performed cholecystogastrostomy in certain cases which they term pseudolithiasis due to cholecystic intolerance, feeling that such an operation gives better results than cholecystectomy. Steel recommends cholecystogastrostomy as a routine procedure in gall-bladder disease in preference to cholecystectomy. Blos has used the operation as a method of obtaining proper drainage in cases of cholangitis with liver infection. Heyd has obtained encouraging results with cholecystoduodenostomy in acute liver degeneration. He reasoned that the operation gave a lymphatic pathway of escape for lymph and edema from the liver.

The object of cholecystogastrostomy in gastric ulcer is, of course, to establish a steady flow of alkaline bile over the ulcer site. Sippy has pointed out, however, that about seven to nine times the normal output of bile would be required to neutralize the gastric juice, since the daily output of bile is about 1000 cubic centimeters the hydrogen ion concentration being 7.4, while the stomach secretes about 1500 cubic centimeters of fluid with a hydrogen ion concentration of 1.2–2.0. Archibald, as a result of animal experimentation, contends that cholecystogastrostomy does not

TABLE II

Cases		No.	
Cholecystoduodenostomies	44	Operative deaths	14
Malignancy	18	Lived 3–16 months	
Chronic pancreatitis, stone	10	Lived 5–30 years	8
		Died cholangitis in 20 years	1
Chronic pancreatitis, no stone	12	Lived (2 for 30 years)	9
		Died of cholangitis	2
Stricture	2		
Cholecystogastrostomies	13	Operative deaths	3
Malignancy	10	(Life average 5 months)	
		Died of cholangitis	2
Chronic pancreatitis, no stone	3	Lived 29 and 14 years	2
Choledochoduodenostomies	58	Operative deaths	5
Malignancy	7	Complete failures	5
		Died of cholangitis 8–17 years	3
Stenosis of common duct	20	Died of other causes	6
		Average 13 years	
		Occasional severe cholangitis	2
Chronic pancreatitis	29	Well 16–30 years	30
		Occasional mild cholangitis	9
Miscellaneous	2		
Hepaticoduodenostomies	13	Operative deaths	5
1 to 4 previous operations			
		Well—24, 11, 10, 4, 1 years	5
		Occasional mild cholangitis	3

divert the flow of bile through the stomach as long as the common duct is not obstructed. The Mayos (48) called attention to this in 1908. Beaver reported that cholecystogastrostomy had no effect upon the gastric acidity in the dog. Kagan, however, gives the data on 3 patients in whom the gastric acidity was lowered after such an operation. Judd and Parker (36) and Babcock (4) agree with this conception. It is perhaps of some interest that Walzel reported a jejunal ulcer following the performance of a cholecystogastrostomy and gastrojejunostomy at one operation.

CLINICAL RESULTS

Although theoretical considerations and laboratory experiments may help a great deal, the final decision as to the value of an operation must come from the actual effect upon the patient. This, however, is not always easy to determine since failures are not so frequently reported as successes.

In the case of cholecystogastrostomy for peptic ulcer, Babcock (3). Braithwaite, Nazarov, and Frenkel report satisfactory results. Frenkel (22) published the only series in which there were follow-up reports. He reported 68 operations with 1 death. Thirteen were not followed. The 54 remaining were followed for from 6 months to 5 years. The results in 35 were classed as excellent, in 11 as fair and in 8 as poor. None of these writers has reported ascending cholangitis as a complication of cholecystogastrostomy for peptic ulcer. This, of course, again brings up the question as to whether the anastomosis persists when the common duct is open. Nazarov reoperated upon 3 of his patients when symptoms returned and he found the anastomosis closed. Since his other cases had no return of symptoms, he assumed that the anastomosis was functioning. Steel had occasion to reoperate upon 4 cases in which cholecystogastrostomy had previously been done for gall-bladder disease without jaundice. The anastomosis was still open in all 4 cases.

The major rôle for biliary intestinal anastomosis comes in cases of common duct obstruction. When the obstruction is due to malignancy, the surgeon performs the anastomosis as a palliative measure. However, when the obstruction is of a non-malignant nature, the surgeon is unwilling to subject his patient to any unnecessary danger such as ascending biliary infection. It is, therefore, of the utmost importance that the success of biliary intestinal anastomosis as to life expectancy be evaluated. If it is true, as some contend, that cholangitis is never a complication, the surgeon can save much time and trouble in the region of the common duct by simply doing a cholecystoduodenostomy or cholecystogastrostomy. On the other hand, if "serious infection of the liver is an almost inevitable consequence" as stated by Graham, Cole, Copher and Moore, the operation must be done only as a last resort.

That the operation is not a cure-all is apparent from the fact that spontaneous biliary intestinal fistulas usually require surgical intervention. As a result of their experience at the Mayo clinic with 153 spontaneous biliary fistulas (117 duodenal) which required operative relief, Judd and Burden (34) concluded that the "formation of a spontaneous internal biliary fistula is in no sense a cure of cholelithiasis, but is an additional and dangerous complication."

In this country, Babcock (3) and Du Bose (18), both of whom have had a large experience with the operation, state that they have never seen cholangitis following cholecystenterostomy. In Europe, Finsterer, Loewenstein, and Bardeleben agree that it is not a

TABLE III.—ANASTOMOSIS OF BILIARY AND GASTRO-INTESTINAL TRACT

Name	Year	Cases	Diagnosis	Longest survival	Remarks
Michaux	1894	1		2 mo.	*Death-cholangitis
Bardeleben	1906	25	Varied	12 yrs.	†
Mayo Robson	1909	64	Common duct obstructed	8 yrs.	‡
Kehr	1913	60	Common duct obstructed		‡
Babcock	1920	130	Varied		† 4 yrs. experience
Mayo, C. H.	1920	13	Common duct obstructed		Hepaticoduodenostomy
Downes	1922	9	Common duct obstructed no stones	4 yrs.	
Mayo, W. J.	1923	104	Common duct obstructed	20 yrs.	Hepatico and choledochoduodenostomy
Du Bose	1923 1932	32	Varied	13 yrs.	†Case of interval jaundice stones
Frenkel	1925	68	Peptic ulcer	5 yrs.	86% satisfactory
Nazarov	1926	30	Gastric ulcer		90% satisfactory
Braithwaite	1926	4	Gastric ulcer		Satisfactory
Berard and Mallet-Guy	1927 1932		Pseudolithiasis	5 yrs.	†
Presno	1927	3	Common duct obstructed	5 yrs.	
Loewenstein	1927	9	Common duct obstructed	9 yrs.	†
Whipple	1927	35	Common duct obstructed		*Of 14 benign cases 4 alive and well
Nassau	1928	3	Common duct obstructed	6 yrs.	Anastomosis obstructed by stone; jaundice
Walters	1928		Stricture	4 yrs.	Barium passed into gall bladder
Judd and Parker	1928	137	Common duct obstructed	6 yrs.	*(See also ref. 35)
Steel	1928	100	Gall bladder disease	8 yrs.	†Operation to replace cholecystectomy
Wangensteen	1928		Common duct obstructed		*1 case cholangitis
Haynes	1929	2	Common duct obstructed	3 yrs.	
Patel	1930	2	Common duct obstructed	10 and 7 yrs.	
Orr	1930	2			*Cholangitis
Lahey	1930	2		7 and 8 yrs.	Transplantation of fistulous tract
Mason and Baker	1931	1		2 yrs.	*Liver abscesses autopsies
Roeder	1931	2		3 mo.	*Liver abscesses autopsies
Leriche and Weiss	1932	2	Common duct obstructed	2 yrs.	
Bernhard	1934	128	Common duct obstructed	30 yrs.	‡
Finsterer	1935	70	Common duct stones	12 yrs.	†
Eliason	1935	10	Common duct obstructed	8 yrs.	*

†Cholangitis never a complication.
‡Cholangitis observed but considered minor hazard.
*Cholangitis considered a major objection to operation.

danger. Gentile, in his recent publication, strongly upheld cholecystogastrostomy as opposed to cholecystoduodenostomy. He stated that not a single case of liver infection has been reported following cholecystogastrostomy. This, of course, is an oversight on his part (45, 60, 12). Finsterer, in a recent address before the Vienna Medical Society, reported 70 cases of stone in the common duct for which he performed cholecystectomy, followed by choledochoduodenostomy with 7 per cent mortality. Of 42 patients followed from 3 to 12 years, 88 per cent were well. He contends that the charge that this operation incurs a danger of ascending infection is unfounded. A number of surgeons, however, who have had a large experience with biliary intestinal anastomosis agree that cholangitis

is a frequent complication, but that its frequency is not great enough to cause the operation to be discarded. Such men are Mayo Robson, Kehr, and Bernhard. Many other writers (26, 69, 35, 45, 60, 72) have considered ascending infection as a major drawback to the operation, and have given case reports in which multiple small periductal abscesses were found in the liver at autopsy.

Bernhard made a report of 128 cases which have a more complete follow-up than those of any other report in the literature. It is given in detail in Table II.

Table III gives briefly the experience of some of the writers as reported by them. It also includes the interval since operation in the longest followed case. The feeling of the writers in regard to cholangitis as it affects life expectancy is noted.

In Table III 10 cases previously unreported are given under the name of the senior author. Malignancy was the cause of the common duct obstruction in half of the cases. The results are as follows:

	Cases
Died in the hospital	4
Died of cholangitis 1 year after operation	2
Not traced	1
Well 6 and 3 months after operation (latter malignant)	2
Well 8 years after operation	1

One of the patients who died from cholangitis had a carcinoma of the bile ducts at the junction of the cystic and hepatic ducts. A hepaticoduodenostomy was done. At autopsy, 1 year later, there was no recurrence of the carcinoma and there were multiple periductal abscesses of the liver. The tube used for the anastomosis was still in place. Autopsy was not performed on the second cholangitis case, but the clinical picture was typical. The patient well at 6 months was a case of stone in the common duct. The stone could not be removed by choledochostomy so at a second operation a cholecystoduodenostomy was done. The fistula from the common duct was also transplanted into the duodenum. The patient well 8 years after operation had a traumatic stricture of the common duct. A cholecystoduodenostomy was done. About 2 years after operation, the patient was severely jaundiced for 3 months but recovered spontaneously. She has had no jaundice since then. A recent X-ray film showed that the tube used for the anastomosis was no longer present.

CONCLUSIONS

1. The operation cholecystogastrostomy or cholecystoduodenostomy has a definite place in surgery in cases of common duct obstruction.

2. Its usefulness in other conditions can not be properly evaluated at the present time.

3. In cases of malignant obstruction of the common duct, the life expectancy may be increased only a few months on the average. Life is made more bearable, however, by the relief of the jaundice.

4. In cases of non-malignant obstruction of the common duct, the life expectancy has been normal in many instances. A number of patients have died within a few years, of ascending liver infection. The average life expectancy cannot be accurately evaluated.

5. Ascending liver infection is a frequent enough complication of the operation to prevent its indiscriminate use.

6. In a poor surgical risk, cholecystogastrostomy or cholecystoduodenostomy is preferable to a long surgical procedure, especially when the removal of the common duct obstruction may be difficult or impossible.

REFERENCES

1. ALEXANDROFF. Die Bewertung der Gallenblasenanastomose mit den Magendarmkanal bei Verschluss der Gallengaenge. Dissertation, Pietrograd, 1921. Quoted by Marinelli.
2. ARCHIBALD, E. Does cholecystenterostomy divert the flow of bile from the common duct? Canadian M. Ass. J., 1912, 2: 557–562.
3. BABCOCK, W. W. Cholecystogastrostomy and cholecystoduodenostomy. Am. J. Obst. & Gynec., 1920, 1: 854.
4. Idem. Control of hyperchlorhydria and its consequences by cholecystogastrostomy. Med. Rec., 1920, 98: 476.
5. BARDELEBEN, A. Erfahrungen ueber Cholecystektomie und Cholecystenterostomie. Jena, p. 46–52, 1906. Quoted by Wangensteen.
6. BEAVER, G. M. Cholecystogastrostomy, an experimental study. Arch. Surg., 1929, 18: 899–912.
7. BÉCLÈRE, H. Deux cas de cholécysto-gastrostomie avec reflux baryté dans la vésicule biliaire. Bull. et mém. Soc. de radiol. méd. de Par., 1934, 22: 95–96.
8. BÉRARD, L., and MALLET-GUY, P. Physiologie et technique de la cholécysto-gastrostomie. J. de chir., 1928, 31: 321–339.
9. Idem. Résultats éloignés d'une cholécystogastrostomie pour syndrome bilio-hepatique. Lyon chir., 1927, 24: 83–86.

10. Idem. Résultat éloigné d'une cholécystogastrostomie pour un syndrome vésiculaire douloureux déterminé par un état pathologique de la voie biliaire principale (vesicule intolerante). Lyon méd., 1930, 145: 573–577.
11. Idem. Résultats éloignés de cholécystogastrostomie pour syndromes pseudo-lithiasiques (vesicule biliaire intolérate). Lyon chir., 1932, 29: 582–586.
12. BERNHARD, F. Die Frueh- und Spaetergebnisse der Cholecystogastrostomie, der Cholecystoduodeno- und Choledochoduodenostomie bei 128 Faellen. Deutsche Ztschr. f. Chir., 1934, 242: 736–756.
13. BLOS, E. Cholecystoduodenostomy for infection of biliary apparatus. Semana méd., 1923, 2: 1301–1305.
14. BRAITHWAITE, L. K. Surgical treatment of chronic duodenal and gastric ulcer; cholecystogastrostomy as operation of choice for inaccessible gastric ulcer. Lancet, 1926, 1: 900–904.
15. DOWNES, W. A. Chronic obstructive jaundice. A report of 9 cases treated by cholecystogastrostomy. Tr. South. Surg. Ass., 1922, 35: 342.
16. DU BOSE, F. G. Cholecystogastrostomy and cholecystoduodenostomy. Surg., Gynec. & Obst., 1924, 39: 295–302.
17. Idem. Cholecystogastrostomy. South. M. J., 1927, 20: 674.
18. Idem. Gall bladder function with special reference to cholecystogastrostomy and the absence of ascending cholangitis. Ann. Surg., 1931, 93: 736–744.
19. DUJARDIN and BEAUMETZ. Sur quelques symptomes présentés par les individus porteurs de fistules biliaires intestinales et sur les préceptes de thérapeutique et d'hygiène qui leur sont applicable. Bull. Acad. de méd., 1894, 31: 258.
20. FINSTERER, H. Address before the Vienna Medical Society reported by Am. M. Ass. correspondent. J. Am. M. Ass., 1935, 104: 1353–1354.
21. FRENKEL, A. Der Einfluss der Cholecystogastrostomie auf den Magenchemismus beim Magen- und Duodenal-Ulcus. Zentralbl. f. Chir., 1925, 52: 1459–1463.
22. Idem. Ein Klimisch-experimentelles Beitrag zur cholecystogastrostomie beim Magen- und Duodenalulcus. Arch. f. klin. Chir., 1928, 153: 407–434.
23. GAGE, I. M. Changes in the liver following cholecystogastrostomy and cholecystoduodenostomy. Proc. Soc. Exper. Biol. & Med., 1931, 28: 693–695.
24. GATEWOOD and POPPEN, P. H. Cholecystenterostomy from an experimental standpoint. Surg., Gynec. & Obst., 1922, 35: 445.
25. GENTILE, A. Cholecystogastrostomy and hepatitis—an experimental study. Arch. Surg., 1935, 30: 449–475.
26. GRAHAM, E. A., COLE, W. H., COPHER, G. H., and MOORE, S. Diseases of the Gall Bladder and Bile Ducts, p. 443. Philadelphia: Lea & Febiger, 1928.
27. HAYNES, I. S. Practical aspects of gall bladder disease, with report of 2 cases of cholecystogastrostomy. Med. & Surg. Year-book, Physicians Hosp. Plattsburg, 1929, 1: 201–209.
28. HEYD, C. G. Acute liver degeneration; treatment by cholecystogastrostomy, with discussion of clinical, pathological and physiological accompaniments. Am. J. Digest. Dis. & Nutrition, 1934, 1: 203–206.
29. HORGAN, E. Reconstruction of the Biliary Tract. New York: Macmillan, 1932.
30. HORSLEY, J. S., JR. Experimental study of cholecystogastrostomy and cholecystoduodenostomy. South. M. J., 1927, 22: 669–673.
31. JACOBSON, J. H. Anastomosis of the gall bladder to the stomach. Cholecystogastrostomy. Am. J. Obst., 1914, 70: 825–836.
32. JENCKEL, A. Beitrag zur Chirurgie der Leber und der Gallenwege. Deutsche Ztschr. f. Chir., 1910, 104: 1–121.
33. JUDD, E. S. Stricture of the common duct. Ann. Surg., 1926, 84: 404–410.
34. JUDD, E. S., and BURDEN, V. G. Internal biliary fistula. Ann. Surg., 1925, 81: 305.
35. JUDD, E. S., MCINDOE, A. H., and MARSHALL, J. M. Dean Lewis' Practice of Surgery, vol. vii, p. 85–89. Hagerstown, Md.: W. F. Prior Co. Inc., 1933.
36. JUDD, E. S., and PARKER, B. R. Biliary intestinal anastomosis for obstructive jaundice. Arch. Surg., 1928, 17: 1–17.
37. KAGAN, M. Ueber Cholecystogastrostomie bei Magen- und Duodenalulcus nach der Methode von Bogoras. Zentralbl. f. Chir., 1929, 56: 975–978.
38. KEHR, H. Chirurgie des Gallenwege. Neue Deutsche Chir., 1913, 8: 676–689.
39. LAHEY, F. H. External and internal biliary fistulæ following cholecystectomy. Ann. Surg., 1930, 92: 649–657.
40. LEHMAN, E. P. Hepatitis following cholecystogastrostomy. Arch. Surg., 1924, 9: 16–24.
41. LERICHE, R., and WEISS, A. Résultat au bout de deux ans d'une cholécystogastrostomie pour pancréatitis chronique sans ictère. Guérison, Bull. et mem. soc. nat. de chir., 1932, 58: 29–31.
42. LOEWENSTEIN, K. Umgehungsoperationen am Gallenwegsystem Nachuntersuchungsergebnisse. Arch. f. klin. Chir., 1927, 147: 655–663.
43. MARINELLI, F. Colecisti-gastrostomia e colecisti-enterostomia sperimentali. Arch. ital. di chir., 1925, 13: 343–371.
44. MASON, J. T. Technic of cholecystogastrostomy. J. Am. M. Ass., 1930, 44: 29.
45. MASON, J. T., and BAKER, J. W. Cholecystogastrostomy; autopsy 2 years later. Surg. Clin. N. America, 1931, 11: 1105–1110.
46. MAYO, C. H. Jaundice and its surgical significance. Surg., Gynec. & Obst., 1920, 30: 545.
47. MAYO, W. J. Surgery of the hepatic and common bile ducts. Lancet, 1923, 1: 1299–1302.
48. MAYO, W. J., and MAYO, C. H. Keen's Surgery, its Principles and Practice, vol. iii, p. 1028–1031. Philadelphia: Saunders, 1908.
49. MAYO ROBSON, A. W. Certain forms of jaundice capable of relief or cure by surgical treatment with a consideration of cholecystenterostomy based on an experience of 64 cases. Lancet, 1909, 1: 371–374.
50. MICHAUX. Sur une observation de cholecystenterostomie déposée par M. Ricard. Bull. et mém. de la soc. de chir. de Par., 1894, 20: 572–578.
51. MULLER, G. P. Cholecystoduodenostomy. Ann. Surg., 1926, 84: 95–99.
52. MURPHY, J. B. Cholecysto-intestinal, gastro-intestinal, entero-intestinal anastomosis and approximation without suture. Med. Rec., 1892, 42: 665.
53. NASSAU, C. F. Gall stone obstructing cholecystoduodenostomy. Surg. Clin. N. America, 1928, 8: 753.
54. NAZAROV, N. N. Cholecystogastrostomy in gastroduodenal ulcer by Bogoras method. Arch. f. klin Chir., 1926, 141: 559–565; Abst. J. Am. M. Ass., 1926, 87: 1597.
55. ODERMATT, W. Die Intrahepatische Variation des Gallenwege die Ductus hepato-cystic und ihre klinische Belentung. Beitr. z. klin Chir., 1925, 133: 221–236.

56. ORR, T. G. Biliary infection following cholecystoduodenostomy. Kansas City Southwest Clin. Soc. Monthly Bull., 1930, 6 (No. 32): 26–30.
57. PATEL, M. Pancreatite chronique avec ictere et cholecystogastrostomie. Forme anormale de pancreatite chronique. Arch. franco-belges de chir., 1930, 32: 576–577.
58. PRESNO, J. A. Indicaciones y resultados lejanos de la colecistogastrostomia. Rev. de med. y cir. de la Habana, 1927, 32: 31–40.
59. PANNELLA, P. La colecisto-duodeno-anastomosi con tubi di metallo riassorbibile. Arch. ital. di. chir., 1932, 32: 645–657.
60. ROEDER, C. A. Modified cholecystogastrostomy. Arch. Surg., 1931, 94: 311–313.
61. SAIDMANN, M. Eine Methode der Cholecystogastrostomie mit Payrschen Magnesium-Prothesen. Chirurg., 1932, 4: 184–185.
62. STEEL, W. A. Internal drainage of gall bladder as a routine operative procedure. Surg., Gynec. & Obst., 1927, 44: 393.
63. SIPPY. Quoted by Du Bose.
64. WALTERS, W. Cholecystogastrostomy. Surg., Gynec. & Obst., 1926, 42: 825–827.
65. WALTERS, W. Cholecystoduodenostomy for stricture of the common bile duct. Proc. Staff Meet. Mayo Clin., Oct. 30, 1929.
66. WALTERS, W. Stricture of the common and hepatic bile ducts. Surg., Gynec. & Obst., 1929, 48: 305.
67. WALTERS, W. The advantage of the two stage cholecystenterostomy. Surg., Gynec. & Obst., 1929, 49: 376–377.
68. WALZEL, P. Ulcus pepticum jejuni nach gleichzeitig Ausgefuhrter Cholecystogastrostomie und Gastroenterostomie wegen chronischer Pankreatitis. Zentralbl. f. chir., 1931, 58: 2679–2682.
69. WANGENSTEEN, O. H. Cholangitis following cholecystenterostomy. Ann. Surg., 1928, 87: 54–65.
70. WEINBERG, J. A., WALLIN, S. P., and BINGER, M. W. Gall bladder-stomach anastomosis. Surg., Gynec. & Obst., 1927, 45: 795–798.
71. WHIPPLE, A. O. Side tract operations for bile duct obstruction. Ann. Surg., 1927, 86: 540–548.
72. WHIPPLE, A. O. Nelson's Loose Leaf Living Surgery, vol. v, p. 517. New York: Thomas Nelson & Sons, 1928.
73. WILLIAMS, H., and SMITHWICK, R. H. Treatment of biliary fistulæ by direct implantation of the tract into the first portion of the duodenum. Ann. Surg., 1929, 89: 932–945.
74. WINIWARTER, A. Ein Fall von Gallenretention bedingt durch Impermeabilitat des Ductus Choledochus Anlegung einer Gallenblasen-Darm Fistel Heilung. Prag. med. Wchnschr., 1882, 7: 201; 213.

PANCREATIC FISTULA

A Case With Intubation of Wirsung's Duct

WILLIAM H. SNYDER, Jr., M.D., and ROLF LIUM, M.D., Boston, Massachusetts
From the Surgical Service of the Massachusetts General Hospital

THE study of pure external pancreatic secretion in the human being has been confined to the cases with pancreatic fistulas such as follow the drainage of pancreatic cysts, traumatic rupture of the pancreas, accidental injury to this gland during upper abdominal operations, and the intubation of Wirsung's duct. Of the latter we have been able to find only one case in the literature, that of Glaessner (8), who in a resection for carcinoma of the duodenum in 1904 cut across the pancreatic duct and put a tube in it leading to the outside of the abdomen. Because of the rarity of this condition, we wish to report a similar case in which Wirsung's duct was intubated after a resection of a carcinoma of the common duct.

The patient, Mr. F. K., a truck driver of 48, was admitted to the Medical Service on March 31, 1934, complaining of jaundice of 12 weeks' duration. He had been well until 13 weeks before entry when he became somewhat nauseated and vomited 3 to 4 hours after every meal. His local physician took several X-ray films which were negative for gall stones or visible mass. He had lost about 35 pounds in weight since the onset of his present illness.

Physical examination revealed a fairly well developed man deeply jaundiced. The liver edge was felt three fingers below the costal margin. His urine was positive for bile, but the stools were green on several examinations. Wassermann was negative; non-protein nitrogen, 32 milligrams per cent; blood cholesterol, 209 milligrams per cent, Van den Bergh direct reaction 22.50 milligrams per cent; bleeding time 2.5 minutes; clotting time, 9 minutes; sedimentation rate, 38 millimeters in 30 minutes; red blood count, 3,190,000; hemoglobin, 60 per cent (Sahli). X-ray examination of the stomach and duodenum could not establish a diagnosis of carcinoma of the head of the pancreas and a surgical consultation advised exploration.

The patient was explored under local anesthesia, and a firm tumor was palpated at the ampulla of Vater which seemed to be about 1.5 centimeters in diameter and to occlude the common duct. Cholecystoduodenostomy with drainage of the common duct was done (Fig. 1).

The patient made an excellent recovery, his jaundice nearly disappeared, and he gained 10 pounds in weight. Five weeks after the first operation he was operated upon again and a transduodenal excision of a tumor at the ampulla of Vater was done. Pathological studies showed it to be a carcinoma probably originating in the common duct. As the tumor was drawn down through the posterior duodenal wall its upper attachments were found to consist of common duct and the upper portion of this pedicle was tied off. In the lower part of the pedicle a large pancreatic duct had been cut across, which was taken to be the duct of Wirsung, and into it a No. 10 French catheter was inserted and sutured. The incision in the posterior wall of the duodenum was then closed about the tube which was led across the duodenum and through the transverse incision in its anterior wall and out through a stab wound in the abdominal wall. The final arrangement with the tube in place is shown in Figure 1.

With the exception of some pain in the left flank for one day following operation and a mild febrile reaction on the eleventh day, the patient made an excellent recovery and ran a perfectly smooth course. He was discharged home on the twenty-second day after operation. He has since had a local recurrence which necessitated further operative procedure, but he recovered from this satisfactorily and left the hospital in fair condition.

Report of Studies in Pancreatic Juice

During the 11 days following the second operation we obtained pure pancreatic juice from the catheter placed in the duct of Wirsung. Our investigations dealt with (1) quantitative studies, on the output of pancreatic secretion, (2) the effect of drugs on the flow of secretion from the pancreas, and (3) qualitative studies on the enzymatic content and chemical constituency of the pancreatic juice.

1. *Quantitative studies. A. Average daily output.* During the last 4 days of our experiment the patient had an average daily output of 1,167 cubic centimeters, although during this time there was a definite rise from day to day until on the last day we obtained 1,384 cubic centimeters. This represents the response to a fairly adequate diet in a convalescing man of 150 pounds. Chart 1 shows the daily output of pancreatic juice from

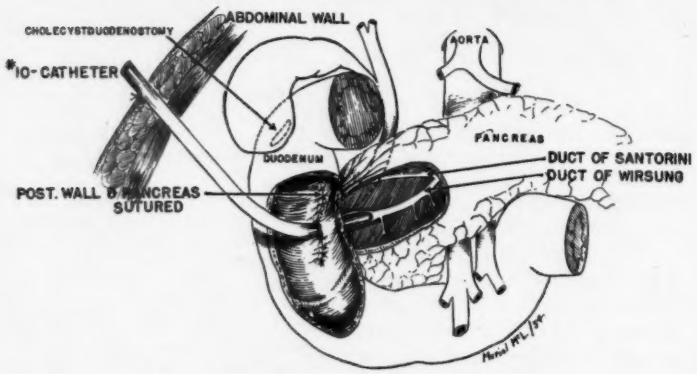


Fig. 1. Anatomical relationships after operation.

8 p.m. to 8 p.m. We are unable to explain the marked decline on the sixth and seventh days, but we know that during this period the response of the organ was grossly irregular when compared with the results obtained on other days.

B. Effect of digestion. Regardless of the activity of the gland, the minute to minute output of the pancreas varies considerably. The number of drops per minute recorded every 3 minutes for an hour while the gland was actively secreting varied from 12 to 26. A perfectly obvious though significant fact is that the main portion of the pancreatic secretion comes during the day when the patient is digesting food. The average output during the day was double that at night. Minute readings were made to determine the time required for the pancreas to respond to a food stimulus. When 65 cubic centimeters of milk were given, the response went in 3 minutes from 5 to 19 drops per minute. The hourly volume for this same feeding is shown in Chart 2. Chart 3 gives graphs for a similar experiment with concentrated glucose and demonstrates a delayed response which might be explained by a slower emptying of the stomach owing to the reflex closure of the pylorus caused by concentrated glucose (Shay, Gershon-Cohen, 28).

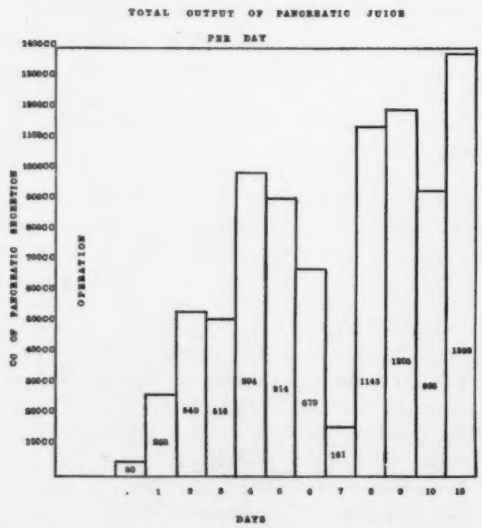


Chart 1. Twenty-four hourly output of pancreatic juice.

C. Continuous secretion. During the last 4 days of our experiment there was only a very rare hour in which there was not at least a few cubic centimeters of pancreatic secretion.

D. Effect of different foodstuffs. It is difficult to draw conclusions from our experiments as to the effects of the 3 main types of foodstuffs upon pancreatic secretion. In analyzing our figures we found only one instance of what could actually be considered a pure meal with adequate control. However we did feed our patient meals composed predominantly of fat, carbohydrates, and proteins and noted the results of pancreatic secretion.

On a fasting stomach we gave 50 grams of glucose in 3 ounces of syrup. The secretion curve is shown in Chart 3 and corresponds

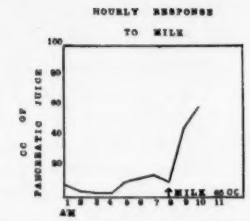


Chart 2. Effect of milk on the response of the pancreas.

closely with those of Holsti and Wohlgemuth except for a slightly delayed response which can be explained on the delayed emptying time of the stomach caused by hypertonic solutions (Shay, Gershon-Cohen, 28).

E. Effect of water. In many instances water given independently of food causes almost immediate stimulation of pancreatic secretion (see Chart 3). This can be explained on the findings of Ivy that if water is placed in the stomach and immediately withdrawn, 5 to 10 cubic centimeters are always lost and have passed along with secretagogues into the duodenum.

2. The effect of drugs. A. Ether narcosis. For 5 hours after ether administration, there was no secretion from the pancreas. This is in accord with experiments on dogs which indicate a depressant effect on pancreatic secretion by ether narcosis (Zucher et al.).

B. Atropine. The results on three experiments with 1/100 grain of atropine given subcutaneously showed the effect illustrated in Chart 4. In addition to a generally diminished output, the expected hourly rise after meals was converted into a diminution by atropine, the duration of its effect being about one hour.

C. Pilocarpine. Pilocarpine seems to increase the output of pancreatic juice. On two occasions 1/100 grain was given subcutaneously and marked increase in the number of drops per minute noted. The duration of its effect was also about 1 hour.

D. Physostygmine. Physostygmine was found to have the same effect as pilocarpine on the one occasion that it was administered in the dose of 1/100 grain.

E. Secretin. We prepared some secretin from the intestinal mucosa of freshly killed

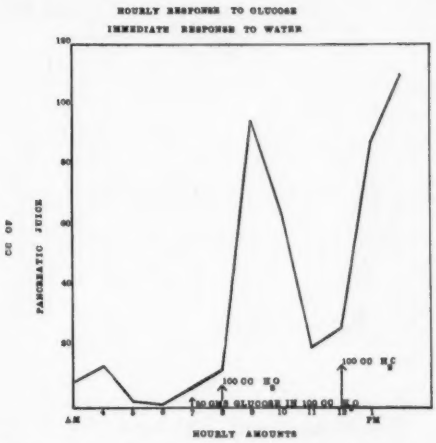


Chart 3. Effect of glucose on the pancreatic secretion.

hogs according to the method of Weaver, Luckhardt, and Koch. After testing it on ourselves for toxic properties we injected 6 milligrams of the purified extract intravenously, but without conclusive results. We prepared a second batch of secretin and intended to give a much larger dose, but the patient refused to have it injected.

3. Qualitative studies. A. Gross appearance. In the main the secretion which we obtained from the pancreatic fistula was a clear, watery fluid. Sometimes it had a slightly ground-glass appearance and contained tiny solid particles. Occasionally it had a slightly yellowish tinge. That this might be due to bile

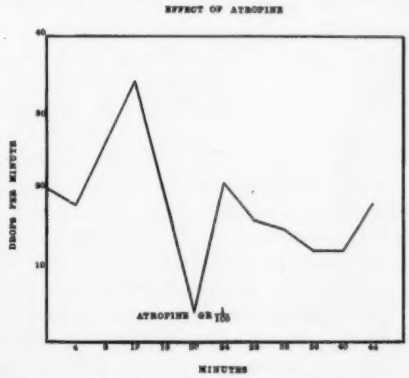


Chart 4. Effect of atropine on the pancreatic secretion.

TABLE I.—AMOUNTS OF PANCREATIC JUICE IN 24 HOURS

Investigator	Volume of secretion in cubic cm.
Ellinger and Cohn	300–442
Glaessner	420–848
Glaessner and Popper	90–250
Graf	30–40
Hohmeier	300
Holsti	90–150
Kahn and Klein	3 days over 1300. Average for 8 days 1120
Karewski	500
Kroiss	Almost one liter.
Maisonnet	230–800 (300–56–800 respectively for three fistulas discussed)
Mocquot	200–425
Monat	500–1000
Pfaff	600
Schumm	292–530
Vilard and Labry	40–185
Villaret and Justin-Besancon	286
Von Friedrich	400–600
Ours	1186

would be possible only by regurgitation from the duodenum (Fig. 1) but we do not believe this to be the explanation since we gave methylene blue by mouth but found no coloring in the secretion secured and furthermore tests on the few yellow specimens obtained with nitric acid and Lugol's solution were negative for bile.

B. Specific gravity. The average specific gravity for all specimens was 1.012. The highest specific gravity, 1.019, was obtained after a 7 hour period of fasting although a high reading was not a constant finding in the fasting secretions. There was no appreciable difference in the specific gravity of the juice obtained after predominantly carbohydrate, fat, or protein meals or after subcutaneous injection of pilocarpine.

C. Reaction and hydrogen-ion concentration. The pancreatic secretion was definitely alkaline. The average hydrogen-ion concentration was 8.6 (10 specimens).

D. Enzymatic action. There were present active lipolytic, amylolytic, and proteolytic enzymes in all the specimens of pancreatic juice examined. We adapted the chemical analysis outlined by McClure, Whitmore, and Reynolds, for estimating the enzymatic activities of duodenal contents and cannot therefore compare our results with those of some of the other investigators in this field (Table III). The lipolytic activity was measured by titrating the amount of butyric acid formed on the addition of the pancreatic secretion to cotton seed oil. Amylolytic activity was based on the production of erythrodextrins in starch solutions and color estimations on the introduction of iodine. Proteolytic activity was based on the determination of the amount of non-protein nitrogen present in a measured amount of casein after the addition of pancreatic juice. A rough estimation of the proteolytic enzymes present was also made by measuring its action on Metz tubes. In 5 millimeter glass tubes there is an average of about 2 millimeters of casein broken down in 24 hours with fresh pancreatic juice. No significant difference occurred with the secretions following special meals. Addition of enterokinase did not increase the activity. The enzymatic activity diminishes on standing in all the samples we examined.

REVIEW OF THE LITERATURE

1. Volume of pancreatic juice. Ellinger and Cohn were the first to notice that the secretion of pancreatic juice in humans is continuous, a finding which has been confirmed by a number of other investigators (1, 9, 12, 14, 30). One observer noted no great difference in secretion between the active and restive states of the patient (12), while another found that on the same dietary regimen 107 cubic centimeters were secreted in the resting condition as compared with 185 cubic centimeters during the active state. Fever diminishes pancreatic secretion (7, 12). As early as 1875 Lacompte showed that pancreatic secretion is least during fasting and most after a meal, and that the increased activity lasts 4 hours after taking food. This finding has been repeated in practically all the cases studied.

We have no accurate figures on the volume of total pancreatic secretion in 24 hours for the human being. Table I shows the 24 hour amount obtained in some of the cases with fistulas which we have reviewed, but it must be remembered that these investigations represent only partial secretion.

The highest figure is that obtained by Kahn and Klein although this is closely approximated by Kroiss and by Monat. Glaessner had a tube in the duct of Wirsung, but this may not mean that total secretion was obtained, in that the duct of Santorini often drains a good part of the pancreatic juice into

TABLE II.—CHEMISTRY OF PANCREATIC JUICE

Author	H_2O%	Total Solids	Sp. gr.	N	Coag. Prot.	Alc. sol. Prot.	Glob.	Alb.	pH	Ash.	Fr. P.
Ellinger and Cohn	98.8618 98.7386	1.1382 1.2614	1.008 1.008	0.084 0.0705	0.1374	0.4240	0.0496	0.0218			
Friedrich	98.749	1.251	1.010 1.013	0.075			0.075	0.152	8.30 F 8.45–8.5	0.5974	0.52
Glaessner	98.7292 98.7516	1.2708 1.2494	1.0074 1.0075	0.0983 0.0842	0.1744 0.1276	0.5080 0.4216	0.0655 0.0410	0.1079 0.0866	after food		
Glaessner and Popper			average 1.009	Kjeldahl 0.504							0.51
Holsti		1.24	1.010 1.013	0.08						0.58	
Kahn and Klein		2–3% 1% org.	1.005						8.2		
Riegner		1.86	1.009								
Schumm	98.4551	1.5449	1.009	0.0804	0.099	0.5611				0.8547	
Vilard and Labry		1.300	1.014							.950	

the duodenum as noted by various investigations (4, 26, 23). The amount obtained from any fistula will necessarily vary with the anatomical location—the largest amounts being obtained when the fistula drains a large duct.

The detailed analysis of the volume output of pancreatic juice has been devoted to a determination of the total amount and secretion curves that result when pure food stuffs are fed. In animals Pawlow found carbohydrate to give the most secretion, protein less, and fat the least. Results in humans have been quite contradictory, but the most reliable bear out the findings derived from animal experiments. There is a group of investigators that found carbohydrate to elicit the least secretion (5, 6) while another reported this type of diet to give the most abundant yield of pancreatic juice (7, 10, 23, 35). Among these reports one finds considerable variation in the diets used and also in most of them a significant amount of the other two food substances in the so called "pure diets." Holsti's conclusions are probably the most reliable and his results in brief are: Carbohydrate yields the most abundant secretion of the pure food stuffs, protein less, and fat least. About the secretion curves he says that the secretion after carbohydrate begins at once, is quite regular and during the observation period is quite active, reaching its maximum in 2 hours. Proteins bring forth an initial rise after which the secretion falls to nothing until the middle of the second hour when it commences with considerable intensity and reaches its maximum in the third and fourth hours. After fat (introduced by a tube) nothing happens before the third hour and then lasts only 1 hour.

One author (35) concludes that the secretion curve after a mixed meal is a composite of those for the individual food constituents making up the meal.

On the basis of his findings, Wohlgemuth introduced a low carbohydrate diet together with large amounts of sodium bicarbonate as an aid in bringing about closure of pancreatic fistulas. In 1908 the same author wrote of several cases collected from the literature in which dramatic closure of the fistula had followed an institution of his so called anti-diabetic regimen. The efficacy of such measures has been confirmed by some (6, 11, 22, 29) and denied by others (7, 17, 30).

2. Chemistry. All investigators agree that pancreatic juice is alkaline and those who have investigated the question find the alkalinity to rise after meals (8, 9). Most authors have found pancreatic juice to be a clear, colorless liquid with small shreds of mucus, but there are notable exceptions where the pancreatic juice was observed to have a yellowish tinge at times (9, 19, 27, 29). In Table II is found a summary of the chemical results reported by the various investigators.

TABLE III.—SHOWING ENZYMATIC ACTIVITY

	After 7 hours fasting	After carbohydrate meal	After cream meal	After egg white meal	Normal duodenal contents (McClure et al)
Lipolytic action	1.10 1.10	1.60 1.60	1.20 1.20	.50	2.4 2.3
Amylolytic action	1.90 1.70	.26 .26	2.90 2.06	2.70 2.70	1.43 1.43
Proteolytic action	2.34 2.60	2.20	2.32 2.10	.94 1.28	2.97 2.99
Proteolytic, plus enterokinase	4.46	1.64	1.94	.74	

Enterokinase alone showed no appreciable proteolytic activity.

All above figures represent determinations based on analysis outlined by McClure, Whitmore, and Reynolds (23).
The specimens were collected on the second hour after the injection of the meal.
All the above specimens were analyzed within 4 hours after taking.
The figures on the lipolytic action indicate the acidity measured in cubic centimeters of tenth normal sodium hydroxide developed in cotton seed oil emulsion by different specimens of 1 cubic centimeter of diluted 1:50 pancreatic juice incubated for 1 hour at 40 degrees C.
The figures on amylolytic action indicate the milligram of sugar developed from soluble starch (44 gm.) by various samples of 1 cubic centimeter of diluted 1:25 pancreatic juice incubated for 30 minutes at 40 degrees C.
The figures on proteolytic action indicate the milligram of non-protein nitrogen developed from casein by various samples of 1 cubic centimeter of diluted 1:50 pancreatic juice incubated for 30 minutes at 40 degrees C.

Glaessner and Popper found pancreatic juice to contain an active hemolysin for dog's corpuscles. Wohlgemuth showed this to be an auto-hemolysin as well as a hetero-hemolysin. He thought it similar to the hemolysin of cobra and other venoms, because like these it is activated by the presence of lecithine. Glaessner and Popper also showed that a subcutaneous injection of pancreatic juice into dogs had little effect whereas after an intraperitoneal injection of 8 cubic centimeters the dogs died within 5 hours.

3. Enzymes. All the cases of proved pancreatic fistula that we have been able to find showed active amyolytic and lipolytic enzymes when these were sought. Both are increased in activity by bile and intestinal juice while the latter is augmented by liver juice and sodium taurocholate. The majority of investigators are agreed that trypsin is secreted in inactive form and this fact explains the failure of pancreatic juice to digest the wound in many instances, for only with active trypsin is this effect noted (14, 19). That intestinal juice converts trypsinogen into active trypsin was first observed in humans by Glaessner (8) whose findings have been corroborated by a great number of observers. There are many substances capable of activating trypsinogen and among them are 1 per cent hydrochloric acid, peptone, bile, liver, liver extract, and calcium chloride.

Of importance in evaluating our results is that contact with air for 1 day (12) as well as that contact with bacteria and bacterial filtrates will also activate trypsinogen. Either of these factors may explain our results of finding active trypsin in our experiments, for no precautions were taken to assure sterile specimens and sometimes 12 hours elapsed before the analysis of enzymes was made.

Rennin or labferment has been found by some (12, 35) and not so by others (8, 9, 27).

Another question in regard to enzymes is their quantitative relationship to the type of food taken. The Pawlow School (25) has been staunch in defending the *Zweckmaessigkeits Prinzip* which holds there is increased lipase secreted in response to a fatty meal, etc. As Pawlow says, "The work of the digestive glands is elastic to a high degree, while it is at the same time characteristic, precise, and purposive." This elasticity has not been confirmed for the secretion of pancreatic juice in humans.

Many observations have been made on humans with the purpose of determining enzymatic response to different types of food (7, 8, 9, 14, 31, 35), but the conclusions reached seem scarcely justified in view of the evidence presented. Here again Holsti's work is exceptional because he used "pure diets" and had a well controlled series of experiments. His conclusions were identical for diastase and lipase, but the results with trypsin were inconclusive, although here the method of analysis might lead to errors in results. For lipase and diastase Holsti concludes: (1) There

are secretions rich and poor in ferments given off by the pancreas. (2) The concentration of enzymes is not dependent upon the rate of secretion. (3) Nevertheless after the same meal in repeated experiments there is a definite relationship between speed of flow and the concentration of enzymes. Although 2 and 3 may seem paradoxical at first reading one realizes on further study that for a given food there will always be a certain concentration of enzymes at a given speed of flow which may be quite different from that of another pure food or a mixed meal. Babkin and Sawitsch (2) find the same true for animals and feel that there is a certain type of juice secreted for each food or mixed meal which is not determined by the speed of flow.

4. Pharmacology. A. Hydrochloric acid. Glaessner showed that a weak solution of hydrochloric acid stimulates pancreatic secretion which commences after a latent period of ½ hour and lasts ½ hour. This has been confirmed by a number of authors (9, 12, 24, 35).

B. Sodium bicarbonate. Glaessner reported bicarbonate as having no effect on pancreatic secretion, but others have noted it as inhibiting the output (11, 15, 25, 40).

C. Atropin. This has a diminishing effect on secretion (8, 12, 29, 30).

D. Pilocarpin. In addition to its enhancing of the secretory state of the pancreas (12, 30) pilocarpin is reported as increasing the proteolytic power of the juice secreted (12).

E. Water. Holsti found that if water is given with the diet there is a different type of secretion curve than without water, but the total amounts are about the same. Only when water is given with food in large amounts (60 cubic centimeters) does it increase pancreatic secretion above that elicited by the food alone.

5. Psychic secretion. The fact that there is an increased flow of pancreatic juice only a brief period after food is taken (in Holsti's case 1 minute after bread, cream, or gruel) has led many investigators to determine whether the pancreas is like the stomach in its response to psychic stimulation. Negative results were reported by several authors. Villaret and Justin-Besancon maintained their patient on a constant diet until he became anorexic, but this influenced the flow of pancreatic juice little when the same food was taken. And when the diet was changed to a more agreeable fare and the patient salivated profusely, the output of pancreatic juice was not increased for 40 minutes even when the patient chewed but did not swallow the food. Similar results were noted by others (7, 14).

Holsti believes that there is a psychic secretion, but his basis for this rests upon an erroneous interpretation of facts. None of his results which cannot be explained by the secondary stimulation by hydrochloric acid of pancreatic secretion.

After reviewing the experiments it seems justified to conclude that if there is any psychic secretion it is only very slight.

6. Diabetes and pancreatic fistulas. Several investigators have noted that a diminished sugar tolerance obtains in cases with pancreatic fistula (7, 12, 22, 23). Holsti and Monat noted that this returned to normal when the fistula cleared up.

SUGGESTIONS FOR FUTURE STUDY

Cases similar to the one reported in this paper as well as those summarized from the literature are quite uncommon. We therefore take the liberty to suggest that future studies may possibly be directed toward solving the following:

The effects of rennin or labferment.

The *Zweckmaessigkeits Prinzip* of Pawlow as it might be applied to humans over a long period of time.

The enzymatic content whether proportional to solid content of pancreatic juice?

The use of Holsti's meals as a standard for test diets.

The estimation of enzymes by Willstatter technique.

The collection of all specimens of pancreatic juice in sterile bottles with immediate chemical and enzymatic studies.

SUMMARY

A case is reported with an intubation of Wirsung's duct following successful resection for cancer of the ampulla of Vater. The largest amount of pancreatic juice obtained in 24 hours was 1,384 cubic centimeters.

Volumetric curves for the digestive phase of pancreatic activity are given. Pancreatic secretion is constant. Of the pure food meals given, only glucose gave reliable results.

Ether and atropin inhibit. Pilocarpin, physostigmine, and water by mouth under certain circumstances stimulate pancreatic secretion.

The physical properties and some chemical analyses of pancreatic juice are given.

Figures for enzymatic content of pancreatic juice are recorded for fasting specimens and those obtained after meals with major portion of one foodstuff. They are not sufficiently numerous to be conclusive. All three enzymes were found in high concentration in all specimens of pancreatic juice obtained.

A review of some pancreatic fistulas as reported in the literature is presented.

Recommendations for further study on human pancreatic fistulas are made.

We wish to thank Dr. Beth Vincent for the use of his case and to acknowledge our indebtedness to Dr. E. D. Churchill and Dr. Chester Jones for their criticisms and suggestions.

BIBLIOGRAPHY

1. Babkin, B. P. Die Aeussere Sekretion der Verdauungsdruesen. 2nd ed., 452–629. Berlin: Springer 1928.
2. Babkin, B. P., and Sawitsch. Ztschr. f. physiol. Chem., 1908, 56: 321–342.
3. Cannon, W. B. The Mechanical Factors of Digestion, p. 89. New York: Longmans Green, 1911.
4. Clairmont, P., and Hadjipetros, P. Deutsche Ztschr. f. Chir., 1920, 159: 251–282.
5. Ellinger, A., and Cohn, M. Ztschr. f. physiol. Chem., 1905, 45: 28–37.
6. Fast, William K. J. Am. M. Ass., 1930, 95: 1668–1669.
7. Friedrich, C. Landislaus von. Klin. Wchnschr., 1922, 1: 1658.
8. Glaessner, K. Ztschr. f. physiol. Chem., 1903–04, 40:465.
9. Glaessner, K., and Popper, H. Deutsches Arch. f. klin. Med., 1908, 94: 46–60.
10. Graf, P. Muenchen. med. Wchnschr., 1910, No. 48, p. 2529–2531.
11. Hohmeier, F. Muenchen. med. Wchnschr., 1907, No. 47, p. 2036.
12. Holsti, O. Deutsche Arch. f. klin. Med., 1913, 111: 48–92.
13. Ivy, A. C. Am. J. Physiol., 1918, 46: 420.
14. Kahn, J., and Klein, H. M. Am. J. M. Sc., N. S. 1932, 184: 503–511.
15. Karewski, F. Deutsche med. Wchnschr., 1890, No. 46a, p. 1035–1037.
16. Idem. Deutsche med. Wchnschr., 1890, No. 47, p. 1069–1071.
17. Kroiss, F. Beitr. zur klin. Chir., 1911, 76: 477–495.
18. Lacompte. Bull. Acad. roy. de méd. de Belg., iii series, 1875, 9: 1023.
19. Maisonnet, M. Bull. et mém. Soc. nat. de chir., 1929, 55: 494.
20. Mayo-Robson, A. W. Brit. M. J., 1908, 1:1153–1161.
21. McClure, C. W., Whitmore, A. S., Reynolds, L. Arch. Int. Med., 1921, 27: 707–715.
22. Monat, Henry A. Med. Bull. Veterans' Adm., 1932, July, p. 83–84.
23. Mocquot, M. Rev. de méd., 1933 April, No. 4, p. 231–245.
24. Opie. Tr. Cong. Am. Phys. & Surg., 1903, p. 1–7.
25. Pawlow, Ivan P. The Work of the Digestive Glands. Translated into English by W. H. Thompson. London, 1902.
26. Pfaff, F. Boston Soc. of Med. Sc., 1898, 2: 10–11.
27. Schumm. Ztschr. f. physiol. Chem., 1902, 36: 292–332.
28. Shay, H., and Gershon-Cohen, J. Surg., Gynec. & Obst., 1934, 58: 935–955.
29. Vilard and Labry. Lyon méd., 1928, 142: 424–428.
30. Villaret, M., and Justin-Besancon, L. Arch. de mal. de l'appar. digest., 1925, 15: 751–767.
31. Walther. Die Sekretorische Arbeit der Verdauungsdruesen. Dissertation, St. Petersburg, 1897. (Quoted by Holsti and Babkin).
32. Weaver, M. M., Luckhardt, A. B., and Koch, F. C. J. Am. M. Ass., 1926, 87: 640.
33. Willstatter, R., Waldschmidt-Leitz, E. et al. Ztschr. f. physiol. Chem., 1923, 125: 93; 1923, 126: 143; 1923–24, 132: 181; 1926, 161: 191.
34. Wohlgemuth, J. Biochem. Ztschr., 1906, 2: 264–270.
35. Idem. Berl. klin. Wchnschr., 1907, No. 2, p. 47–51.
36. Idem. Biochem. Ztschr., 1907, 4: 271–280.
37. Idem. Berl. klin. Wchnschr., 1908, 45: 389–393.
38. Zucher, T. F., Newburger, P. G., and Berg, B. N. Am. J. Physiol., 1932, 102: 193.

PHYSIOLOGICAL CHANGES IN THE URETER ASSOCIATED WITH PREGNANCY[1]

HERBERT F. TRAUT, M.D., AND CHARLES M. McLANE, M.D , NEW YORK, NEW YORK
From the Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital

ANATOMICAL changes in the ureter of the pregnant woman have been a subject of study since 1843 when Cruveilhier first described the dilatation and elongation of the ureter as a frequent accompaniment of the gravid state. We have learned that there is a hyperplasia of the tissues composing the walls of the kidney pelvis, the ureter, and the bladder in the form of increased thickness of the muscular and connective tissue elements. In addition, there is elongation of the ureter and dilatation of the ureter and kidney pelvis. The extent to which these changes take place varies much in different individuals, as well as in the two tracts of the same individual, the process usually being more marked upon the right side.

Two schools of thought have arisen as the result of prolonged attempts to explain this phenomenon. The first and older group has felt that pressure of the enlarged uterus upon the ureters, particularly at those points where the ureter crosses the pelvic brim, was the chief factor. In addition, it has emphasized the frequent dextro-rotation of the uterus as well as the prominent relationships of the large iliac vessels on the right to account for the greater degree of dilatation and elongation usually observed in the right tract. The other school has felt that these anatomical relationships were undoubtedly factors of importance but could not be accepted as the complete explanation, pointing out that larger pelvic tumors than those represented by the pregnant uterus, such as myomas and ovarian cysts, were not often productive of the ureteral changes in the non-pregnant individual. In addition, dilatation of the ureter usually reaches its maximum at about the seventh month of pregnancy, and frequently diminishes toward term, despite the constant enlargement and increasing weight of the uterus. For these reasons, it has been maintained that some other factor than the enlargement of the uterus must exist. Several writers have suggested an atony of the ureteral musculature; however, thus far no one has succeeded in proving atonia to exist although various attempts have been made to do so. Until recently, these have consisted in observing the relative frequency of spurts of colored urine as they emerged from the ureteral orifice into the bladder. These studies have seemed to indicate a definite decrease in the muscular activity of the ureter in pregnancy, but have not been conclusive in that the periods of observation were necessarily short and were not carried out on the same individuals at different stages of pregnancy, so that one could not be sure that the differences noted were not individual variations.

The practical importance of the problem lies chiefly in the relationships of these ureteral dilatations to the incidence of urinary stasis and subsequent infections. Indeed, it would seem to be the most important single factor in explaining the incidence of pyelitis in pregnancy.

Trattner and his associates have perfected an apparatus which makes it possible to observe and record the peristaltic activity of the human kidney pelvis and ureter. Their application of this device has been confined to the ureter of the male and the non-pregnant female. In this study, we have used the Trattner hydrophorograph, as he has named the device. The apparatus consists essentially of a tambour lever and water manometer connected through a two-way stopcock to an intra-ureteral catheter and is equipped with an adjustable escape valve. An electrical counting device records simultaneously the rate of urinary excretion (Fig. 1). By means of an adjustable escape valve, any level of intra-ureteral tension can be maintained or varied at will. The apparatus is equipped with a recording device which produces a permanent record that can be preserved and

[1]Submitted for publication April 1, 1935.

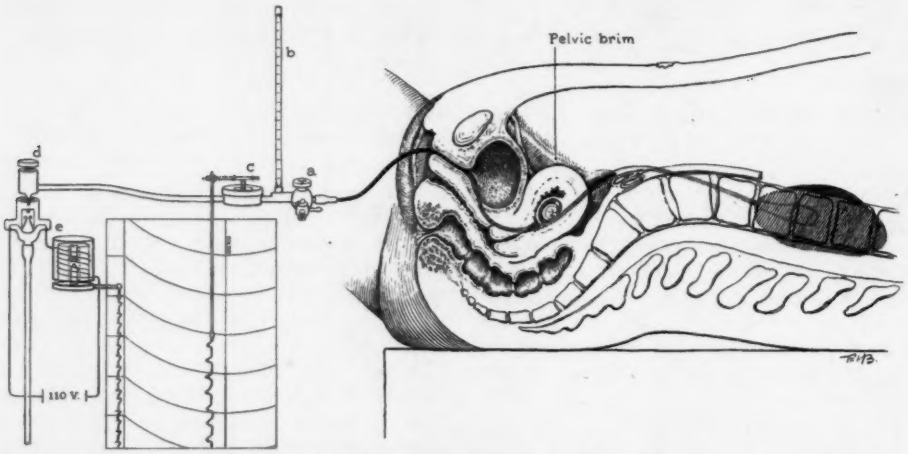


Fig. 1. Diagrammatic drawing illustrating the principle of the hydrophorograph: *a*, three-way stopcock; *b*, water manometer connected with the ureteral catheter and tambour providing visual means of checking pressure levels as well as amplitude of fluid waves resulting from peristalsis; *c*, tambour and writing lever; *d*, adjustable escape valve providing means for controlling intra-ureteral pressure; *e*, electrical drop counting device.

makes possible a comparison of ureteral activity.

Thus far, we have studied 34 women, 27 of whom were pregnant or puerperal, and 7 normal, non-pregnant controls. The relationship of the observations to the various stages of pregnancy are expressed in the accompanying table (Fig. 2).

It has been possible for us to make repeated observations at monthly intervals on 12 of the 27 pregnant women whose ureters were studied. All of the deductions that have been made concerning variations in the physiological activity of the ureter in the different periods of pregnancy are based upon the study of this group of patients. The remaining 15 upon whom one observation, or at the most, two were possible, have been used cautiously because of the variation that exists between individuals. For the most part, they were found to conform to the characteristics of the various types of curves and their incidence in pregnancy as established by the more intensively studied group, and therefore, they have been included in this report as cumulative evidence.

Each time a hydrophorograph record was taken a retrograde pyelogram was made with the injected contrast medium under as nearly the same pressure as possible. The object in

	Non-Pregnancy	PREGNANCY			Postpartum
		1st Trimester	2d Trimester	3rd Trimester	
Normal curve	|||||| (7)	||| (3)	|||||||| (8)	||||| (5)	|
Modified curve		|	||||| (5)	||||| (5)	|
Flat curve		|	||| (3)	|||||| (7)	|| (2)

Fig. 2. Indicating the number and distribution of observations of normal, modified and absent ureteral response.

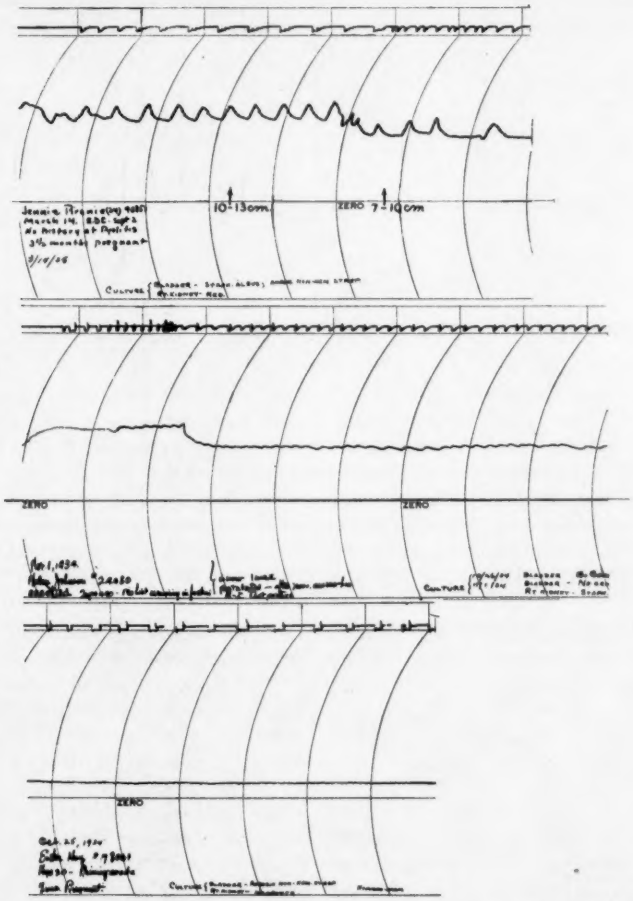


Fig. 3. Actual ureteral tracings illustrating normal, modified, and absent response.

making the roentgenogram was to ascertain the relationship between dilatation of the ureter and loss of peristaltic activity on the one hand, and, on the other, to control accurately the distance the catheter was allowed to ascend the ureteral tract. The upper end of the catheter was kept as nearly as possible at the upper margin of the pelvic brim. In this way, we have compared that portion of the ureter lying above the pelvic brim in all patients whether in late or early pregnancy. Wislocki and O'Connor showed in their ureteral experiments upon dogs that activity of the organ depended upon, and varied tremendously with, the rate of urinary secretion. In other words, it is necessary to provide the ureter with an adequate mass to propel. Therefore, we have made certain that all our patients ingested large amounts of water during the hour preceding an observation and have attempted in this way to obviate a source of possible error.

After catheterizing the right ureter, the catheter was immediately connected with the hydrophorograph and a record made of the rate of urinary excretion simultaneously with

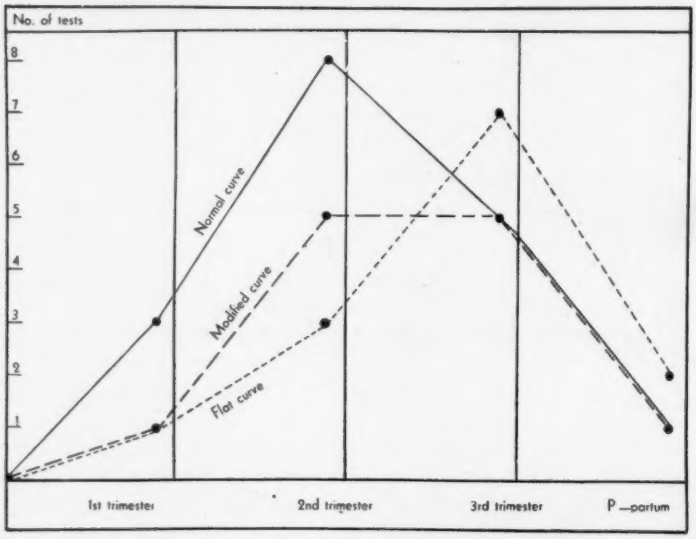


Fig. 4. A graphic representation of the data contained in Figure 2, excluding the non-pregnant group, showing the incidence of normal and modified response with respect to the various trimesters of pregnancy.

one of the peristaltic pattern of the ureter. We found that the ureter response varied with the intra-ureteral pressure, that of the normal non-pregnant individual being maximal at pressures lying between 4 centimeters and 12 centimeters of water pressure. For the purposes of our study, we commenced at a pressure slightly higher, namely, 15 centimeters of water pressure, and then dropped this by successive stages to 10 centimeters and 5 centimeters, maintaining each level for approximately 3 minutes and recording the ureteral response at each level. In this manner, we have hoped to offer the optimum conditions for muscular response in each case.

Months of pregnancy

	1st	2d	3rd	4th	5th	6th	7th	8th	9th
Normal curve		I	II	IIII	II	II	II	II	I
Modified curve			I	II	I	II	II	II	I
Flat curve			I		I	II	III	III	I

Fig. 5. The distribution of the three types of ureteral curves with respect to the various months of pregnancy.

The presence of urinary tract infections has been ruled out by taking ureteral and bladder urine cultures at the time each observation was made. This seemed important as it has been demonstrated that during the acute phase of an infection, peristaltic activity may be increased, whereas during the chronic phase, it may be depressed or absent. All patients included in this study had consistently negative ureteral bacterial cultures.

As will be seen from a study of the graphs, we observed three general types of variation in the peristaltic record. The first is a regular rhythmic curve of fairly uniform amplitude of excursion at all levels of pressure; this is considered normal. The second shows a lesser degree of excursion with a greater response, usually at one level or another, as well as irregularity in the degree of excursion; this group we have characterized as modified response and have found it to be frequent in the earlier months of pregnancy. The third is characterized by a total lack of rhythmic muscular contraction at any level and has been found to be a frequent observation in

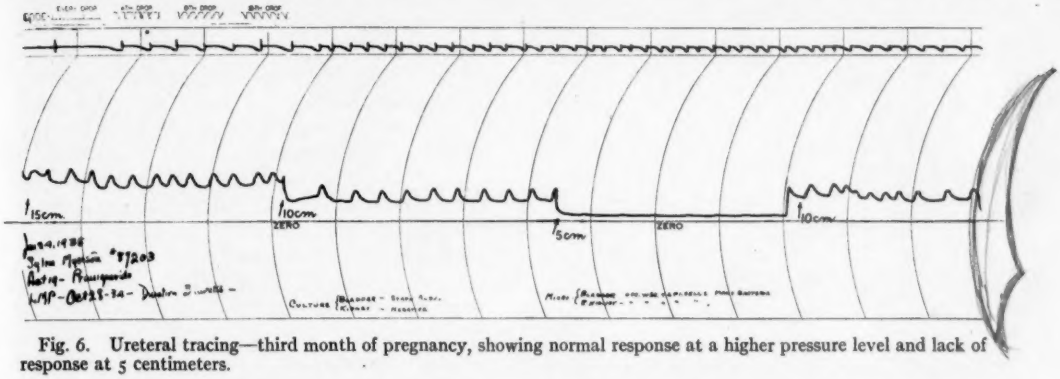


Fig. 6. Ureteral tracing—third month of pregnancy, showing normal response at a higher pressure level and lack of response at 5 centimeters.

the latter months of pregnancy (Fig. 3). The incidence of these three types of response with respect to the various periods of pregnancy are portrayed graphically in Figures 4 and 5.

From this, it will be seen that, during the first and second months of pregnancy, ureteral activity is quite normal. With the passage of the third and fourth months, the incidence of modified ureteral response becomes more marked, whereas during the sixth, seventh, and eighth, modified response or total lack of response becomes the rule. During the ninth month, there is evidence of a returning irritability in the form of more adequate muscular activity.

The foregoing statement is the result of our experience in most instances. However, not all patients show diminished peristalsis as indicated. A small minority (2 in our whole series of 34 cases) maintained normal ureteral activity throughout pregnancy (Fig. 5).

The most constant early change observed was the disappearance of peristalsis when 5 centimeters of water pressure was maintained within the ureter, after the ureter had responded well at the higher levels of 10 centimeters and 15 centimeters. This observation seems to hold good regardless of the degree of ureteral dilatation and also the rate of urinary secretion (Fig. 6).

We have given a great deal of thought to the possible causes of this variation in the ureteral peristaltic activity associated with the various phases of pregnancy. It is well known that slight distention of a hollow viscus capable of peristalsis, stimulates that organ to increased activity, whereas overdistention obliterates its power of rhythmic contraction for a time, but there will be a return of this property provided the distention has not been excessive and has not persisted for too great a period of time. For this reason, we have

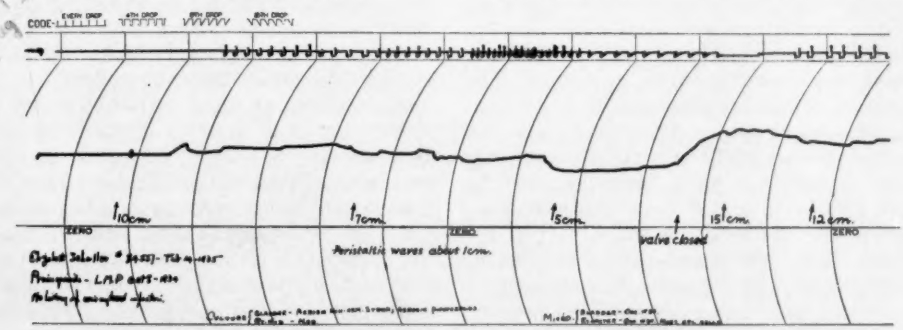


Fig. 7. Tracing at fourth month of pregnancy showing markedly modified peristalsis even though the secretion of urine (24 drops per minute) is rapid.

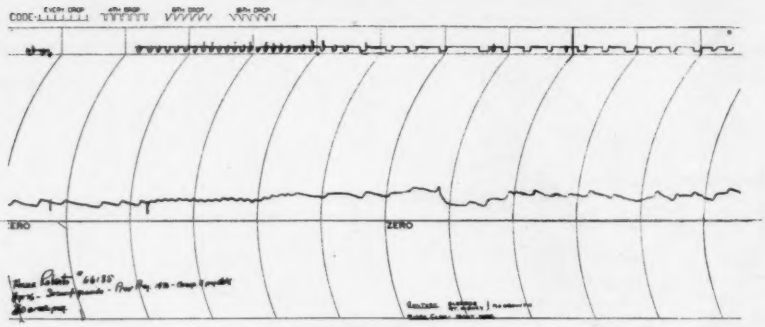


Fig. 8. Tracing taken during the seventh month of pregnancy, demonstrating modified muscular activity with rapid excretory ability in a widely dilated ureter.

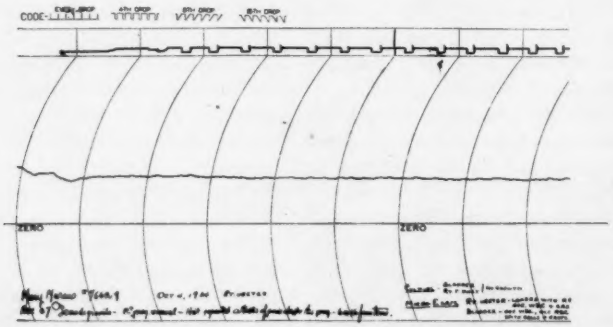


Fig. 9. Eighth month of pregnancy showing completely atonic ureter. Note excretion of urine is 8 drops per minute.

studied the pyelograms of these ureters hoping that there might be a close parallelism between dilatation of the ureter as an expression of prolonged distention and the incidence of modified or absent peristalsis. Thus far we have failed to find any such relationship, particularly during the second, third, fourth, and fifth months of pregnancy, when the process is supposedly in its incipiency. The degrees of dilatation observed as a concomitant of normal pregnancy may or may not be associated with loss of peristaltic activity.

A few instances have been observed in which very widely dilated ureters were possessed of normal muscular activity (Fig. 8). We are, therefore, forced to the conclusion that the weight of the enlarged uterus upon the ureters with embarrassment of urinary outflow and subsequent dilatation, is associated with loss of muscular activity in varying degree but is not its cause. The observation that there is at least a partial return of peristalsis during the ninth month (Fig. 10), is final, convincing proof of the correctness of this opinion. One is forced to conclude that there must be another cause of atony of the ureter in pregnancy, and that the loss of muscle tone is contributory to the dilatation of the ureter rather than the reverse.

Inasmuch as we know little concerning the possible causes of ureteral atony in the pregnant woman, it may be of profit to apply speculatively some of the facts that have been gleaned concerning other organs the walls of which are composed mainly of smooth muscle. For example, Westphal has demonstrated a marked diminution in the muscular irritability of the gall bladder in pregnancy. Hofbauer, pursuing this line of investigation, demonstrated that hypertonic solutions of cholesterin

salts produced this effect and argued that inasmuch as the blood of the pregnant woman contained markedly increased amounts of these salts, this was a possible explanation of the phenomenon.

The large bowel is another structure of the body which has been demonstrated to undergo marked regression of its muscular response during pregnancy. This observation has long been invoked as the explanation of the constipation experienced commonly during the latter months of pregnancy, but thus far no more rational etiological factor has been advanced than that of the weight of the pregnant uterus, which, in view of our studies on the ureter, does not appear to be an adequate explanation.

The outstanding example of smooth muscle atony of a hollow viscus in pregnancy is, of course, the uterus. In this organ loss of muscular irritability is the most important single factor in insuring the successful fruition of pregnancy. Knaus has shown rather conclusively that one substance capable of producing this effect on the uterus is the hormone of the corpus luteum, progestin. Whether this is the only substance instrumental, or even the most important one, seems doubtful, because we know that removal of the corpus luteum from the body of the pregnant woman after the third month is not accompanied by a prompt return of contractility on the part of the uterus, with resulting abortion.

It would seem likely that the body had been provided with a superabundance of some substance capable of producing atony in smooth muscle for the purpose of safeguarding pregnancy and that its effect is not entirely specific for uterine musculature but, in addition, possesses a modified, though similar, action upon other structures. At this time, we must content ourselves with speculation upon the subject, though we hope at some future time not only to present a more complete picture of the effect of this phenomenon but, in addition, to offer some evidence as to its nature and mode of action.

CONCLUSIONS

1. The normal ureter of the non-pregnant woman is possessed of rhythmic peristaltic activity which can be measured and recorded.

2. This rhythmic peristaltic activity is definitely altered by pregnancy in varying degrees in the majority of our patients (34) studied.

3. This altered peristaltic activity is expressed by diminished amplitude of the peristaltic wave, commencing in the third month of pregnancy, but reaching its peak during the seventh and eighth months.

4. After the fifth month the number of patients showing diminished ureteral response exceeds those showing normal activity.

5. During the last month of pregnancy there seems to be a definite return of muscular irritability as expressed by the measurement of peristalsis and response to stimulation.

6. This diminished peristaltic activity of the ureters seen in pregnancy cannot be explained on a basis of dilatation. On the contrary, dilatation of the ureters during pregnancy is probably in great part dependent upon the atony of the ureters.

7. The etiology of this observed ureteral atony during pregnancy is, in our opinion, not dependent upon any mechanical factor but rather upon some, as yet unexplained, chemical basis.

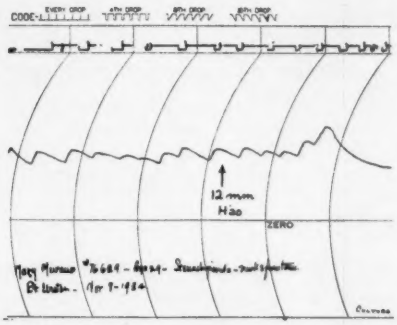


Fig. 10. Tracing of same ureter as illustrated in Figure 9, one month later (ninth month) demonstrating a remarkable return of ureteral activity.

BIBLIOGRAPHY

1. BAIRD, D. A study of ureteral tone during pregnancy. J. Obst. & Gynæc., Brit. Emp., 1933, 40: 472.
2. JONA, J. L. A further contribution to the physiology and pathology of the kidney pelvis. Surg., Gynec. & Obst., 1934, 59: 713.

3. KREUTZMANN, H. R. Studies in normal ureteral and vesical pressure. J. Urol., 1928, 19: 517.
4. ROSE, D. K. Determination of bladder pressure with a cystometer; a new principle in diagnosis. J. Am. M. Ass., 1927, 88: 151.
5. STOECKEL, W. Betrachtungen ueber die Pyelitis gravidarum. Muenchen. med. Wchnschr., 1924, 71: 257.
6. TRATTNER, H. R. Graphic registration of the function of the human ureter. J. Urol., 1932, 28: 1.
7. WISLOCKI, G. B., and O'CONNOR, V. J. Experimental observations upon the ureters. Johns Hopkins Hosp. Bull., 1920, 31: 197.
8. WUELLENWEBER, G. Untersuchungen ueber den Nicrenbeckendruck, besonders in der Graviditaet. Klin. Wchnschr., 1930, 9: 295.

CLINICAL SURGERY

RECONSTRUCTIONS ABOUT THE NASAL TIP[1]

CLAIRE L. STRAITH, M.D., F.A.C.S., DETROIT, MICHIGAN

WITH the broad experience gained from the treatment of increasing numbers of nasal deformities of all grades of severity, procedures for their correction have been greatly improved within recent times. As a result, the patient requiring rhinoplasty, whatever the degree, can now be assured of a cosmetic or functional result sufficiently satisfactory to enable him to resume his rightful place in society. Properly selected operations, skillfully performed and adroitly adapted to the circumstances presented by the individual case, will do much to prevent the telltale secondary blemishes which are painfully apparent to patient and observer. Routine adherence to the older methods, however excellent their principles or hallowed their tradition, is not desirable in all instances and will produce results far inferior to those attainable through the individualistic use of more modern procedures.

The purpose of this communication is to demonstrate the feasibility of successful rhinoplastic reconstruction without recourse to extrafacial sources for skin grafts, avoiding at the same time, unsightly secondary facial blemishes. A new technique for the correction of nasal depressions, which accomplishes its purpose without the necessity of external incisions or free cartilage transplants, is also presented. The accompanying photographs illustrate the wide variety of nasal deformities resulting from dermal, soft tissue, and supporting structure defects which are amenable to plastic reconstruction with the methods employed by the author.

It would be unjust to deny the value and general dependability of the classical methods of rhinoplasty. Despite their obvious drawbacks, they are still indicated in certain types of cases. The Indian, or forehead flap, method, while an excellent means in women for covering major nasal defects with skin of suitable color and texture, has definite disadvantages in the male. This method in men practically resolves itself into a matter of exchanging an ugly nasal defect for a less unsightly though nevertheless visible forehead scar. This scar, despite successful skin grafts, continues as an obvious blemish unless it can be hidden by the overhanging hair. In persons with low foreheads, a portion of the flap is usually covered with coarse hairs. Attempts to remove these hairs are often unsuccessful, difficult, or frankly dangerous (X-ray). The Italian, or arm flap method should be mentioned only to be con-

Figs. 1 and 2. Perforation of nasal tip. Defect covered by Wolfe graft of skin which was taken from the upper eyelid.

Figs. 3 and 4. Recent full thickness skin defect. Restoration 48 hours after injury using a Wolfe graft of skin from behind the right ear.

[1] Read before the Society of Plastic and Reconstructive Surgery, New York, October 10, 1934.

Figs. 5 and 6. Loss of right ala. Restoration by skin flap from side of nose. Less secondary scarring is produced by method illustrated in Figures 19–21.

demned. The skin provided has a color and texture which differs markedly from that of the facial integument. The presence also of large amounts of subcutaneous fat interferes with molding and, according to some, with proper healing as well. The necessarily prolonged maintenance of the arm before the nose during the grafting period is a source of great discomfort to the patient and is not without danger of permanent arm damage through subsequent contractures.

To be acceptable, a surgically reconstructed nose must have a covering of smooth skin of normal color, a contour which harmonizes with the face, a functional epithelial lining, and an adequate airway. Infectious or malignant processes must be eradicated before repair is commenced; distorted tissues must be freed and replaced. In the plastic reconstruction, each damaged or missing component and anatomical structure (lining, covering and supporting framework) must be restored. The ideal toward which the surgeon must strive is complete anatomical and physiological restoration with a minimum of residual or secondary scarring.

For reconstructions about the nasal tip, the author makes use of the following methods, the choice being determined by the nature and extent of the lesion (dermal, soft tissue, or supporting structure defects):

SKIN AND SOFT TISSUE DEFECTS

1. Small skin defects are readily covered by Wolfe grafts obtained from the upper eyelid or posterior aspect of the ear. This method is particularly useful when repair of surface skin defects is attempted shortly after injury (Figs. 1–4).

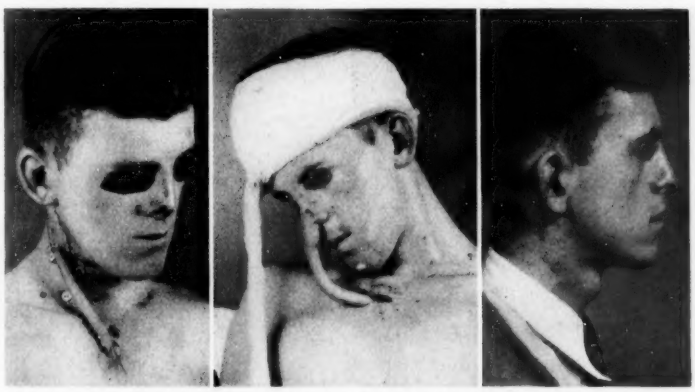
2. Defects of the ala nasi may be corrected by delayed pedicle flaps rolled down from the side of the nose, the normally rounded alar border being formed by the rolled edge. The resulting defect at the side of the nose is then covered by a Wolfe graft (Smith). This method is best reserved for small lesions (Figs. 5–6). Restoration of the base of the ala may also be accomplished by delayed pedicle transfers from the region of the nasolabial folds (Figs. 7–9). A slight though nevertheless visible facial scar is the only objection to this method.

3. Skin and soft tissue losses at the nasal tip in women, especially when extensive, are best treated

Figs. 7, 8, 9. Loss of left ala, distortion of nasal tip and partial obstruction of nostril. Correction by means of pedicle graft from left nasolabial fold. Nasal lining formed by invaginating tip of graft into the nostril. The scar in the nasolabial fold is scarcely visible.

Figs. 10, 11, 12. Loss of nasal tip in motor accident. Restoration by forehead flap nourished by left temporal artery. The forehead scar after Wolfe grafting is concealed by the hair dress.

Figs. 13, 14, 15. Nasal amputation to remove carcinoma of the nasal tip. Reconstruction of nose 1 year later by Indian method. Secondary forehead scar after Wolfe grafting concealed by hair dress.



Figs. 16, 17, 18. Loss of skin over bridge, tip, and alæ. Author's method for restoring nasal skin in males. Unsightly forehead scars are avoided.

Figs. 19, 20, 21. Loss of right ala as result of dog bite. Restoration by author's method. Nasal lining provided by inverting the distal portion of the flap.

by forehead flap transfers, either by pedicles nourished by the temporal artery (Figs. 10–12), or by the classical Indian method (Figs. 13–15). The axis of the flap and its situation on the forehead should be determined by the location and extent of the lesion as well as by the patient's style of hair dress. A nasal lining is provided from the skin surrounding the defect or by the application of Wolfe grafts to the under surface of the forehead flap before its transfer to the nose. The forehead scar which remains after Wolfe grafting is concealed by the hair.

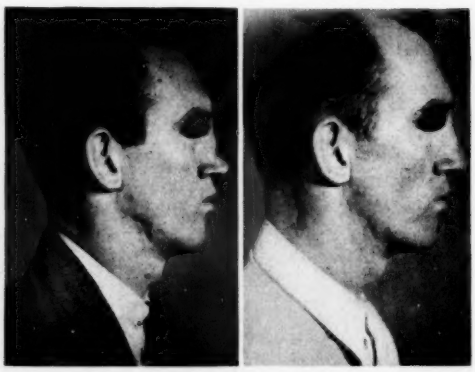
The disadvantage of this method in men lies in the inability, except in unusual cases, to conceal the forehead scar by the hair. To avoid these unsightly scars in men, the author has devised a method of rhinoplasty by means of which, skin from below the ear may be transferred to the nose on a tube pedicle via the sternal notch. Since its original publication,[1] the author has performed this operation successfully in several additional cases with very gratifying results. This method has several distinct advantages: (1) forehead scars are avoided, (2) the skin matches the nasal integument and is practically hairless, (3) the skin is thin and easily molded to shape, (4) the resulting neck scar is inconspicuous (Figs. 16–21).

SUPPORTING STRUCTURE DEFECTS

In cases requiring reconstruction of the cartilaginous portion of the nasal bridge, use

[1] Rev. d. chir. plastique, 109-115, August, 1933.

Figs. 22 and 23. Defect in nasal bridge resulting from septal abscess following bee sting. Depression filled in by insertion of pieces of ear cartilage through mid-columellar incision.



Figs. 24 and 25. Depression of cartilaginous bridge and nasal tip resulting from fall in infancy. Correction of this deformity was obtained by inserting hinged rib cartilage transplant.

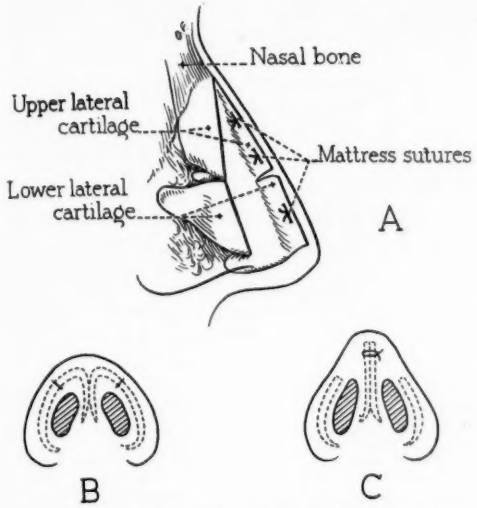


Fig. 26. *A*, Diagram illustrating author's method for raising nasal bridge by everting upper lateral cartilage flaps. *B* and *C*. Diagram illustrating Kazanjian method of raising and narrowing nasal tip by using flaps of alar cartilage. The author combines this procedure with *A* to correct depressions of the nasal tip and bridge.

should always be made of cartilage rather than prosthetic inserts of foreign substances (ivory, etc.). Cartilage is not absorbed and has the advantage of being readily shaped and easily grafted. The cartilage can be obtained from several sources, the choice of which is determined by the nature and extent of the defect.

1. *Depressions of the cartilaginous bridge* associated with prominence of the nasal tip can be filled in by one or more pieces of ear cartilage inserted through a mid-columellar incision (Figs. 22–23).

Fig. 27. Illustrating author's method of maintaining upright position of newly formed cartilaginous bridge by means of mattress sutures of horsehair passed through the cartilage flaps and tied over gauze rolls for one week.

2. *Broadly depressed cartilaginous bridges* associated with overhanging flattened nasal tips can be treated by several methods:

A. Hinged or mortise-jointed rib cartilage transplants may be inserted so that the vertical support rests upon the maxilla; the horizontal arm is shaped to correct the defect in the nasal bridge (Figs. 24–25).

B. The introduction of rib cartilage transplants for depressions of the cartilaginous bridge can be avoided by the use of the author's recent extension of the principle of the Kazanjian operation (eversion of the lateral wings of the alar cartilage and suturing them back to back to support the nasal tip). The author augments this procedure by including also the upper lateral cartilages

Figs. 28 and 29. Early childhood injury, resulting in flattened nasal tip and bridge. Front view showing nose before and after correction by author's method (see Figs. 26 and 27).

Figs. 30 and 31. Profile view of preceding case showing broad, drooping nasal tip. Shortening of nose, elevation and narrowing of nasal tip and bridge accomplished in one operation. (Author's method.)

which are first cut, according to the depth of the bridge depression and then everted. They are next stitched back to back with two sutures of chromic catgut. Horsehair mattress sutures passed through the everted cartilage flaps and tied over rolls of gauze help to maintain their upright position (Figs. 26–27). The horsehair sutures are removed in 1 week.

This method combined with that of the Kazanjian operation (which merely elevates and narrows the nasal tip) has produced excellent corrections of overhanging flattened nasal tips associated with broadly depressed cartilaginous bridges. It has the advantage of eliminating the necessity of rib resections as a source of cartilage, a disabling procedure which is not devoid of danger. It also forms a more flexible and natural nasal bridge than is obtained from the use of rib cartilage transplants. Moreover, the advantage of permitting the surgeon to shorten the nose and to elevate the bridge in a single stage operation without the necessity of external incisions, represents a distinct advantage over the more complicated and hazardous procedures hitherto described. The absence of a nasal septum strong enough to support the everted cartilages is an important contra-indication to this procedure (Figs. 28–31).

SUMMARY

1. The correction of deformities about the nasal tip demands carefully individualized management if ideal results are to be attained. The operation should be adapted to the patient, not the patient to the operation.

2. Operations providing facial skin and a minimum of secondary deformity are most desirable.

3. The author describes his method for restoration of the nasal tip, and his technique for correction of bridge defects by means of upper lateral cartilage flaps.

MALUNITED FRACTURES AFFECTING THE ANKLE JOINT

With Special Reference to Twenty-two Cases Treated by Arthrodesis

A. GURNEY KIMBERLEY, M.D., New York, New York
Fellow of the New York Orthopædic Dispensary and Hospital

MANY ankle joints of which the anatomy and function have been disturbed by fractures continue to give symptoms long after the fracture has healed. To insure a symptomless ankle one must obtain union of the fracture with complete reposition of the talus directly under the axis of weight bearing and anatomical restitution of the joint topography.

The writer has reviewed the records of all of the 216 patients who entered the New York Orthopædic Dispensary and Hospital during the years 1928 to 1933, inclusive, with malunited fractures affecting the ankle joint. These patients, with four exceptions, had their initial treatment elsewhere, but because of continued symptoms had looked to other sources for relief. The lapse of time since fracture ranged from a few weeks to many years, in most instances more than 6 months.

Failure to secure and retain complete reduction had resulted in symptoms varying from a dull ache present only at weather changes to a constantly painful ankle causing the patient to walk with a protective limp and to resort to a cane or crutch. Physical findings varied from the apparent normal to a greatly swollen, cyanotic ankle and foot with limited and painful motion, tenderness over the fracture sites and anterior surface of the joint, and distortion of the ankle mortise. In the latter, dorsiflexion was often greatly limited, so that the patient either bore weight on the forefoot only or, to get the heel to the ground, hyperextended the knee and externally rotated and abducted the hip.

Eighty-eight per cent of the fractures had occurred in adults; of these 71 per cent were in females, whereas among those under 18 years of age boys predominated over girls in the ratio of five to four. The more common occurrence in women is too great to be ignored, especially since men are more subject to traumatic injuries. This may be due to ankle instability incident to wearing high heels.

NON-OPERATIVE TREATMENT

These patients were usually treated by means of a metal or rubber plantar arch, exercises, contrast baths, and massage. Occasionally such measures as an inner heel wedge, ace bandage, adhesive strapping, and baking were used. Salicylates were sometimes given for relief from pain, and for the obese a reduction diet prescribed.

Of these measures none helped more than a metal arch patterned on a plaster mold of the foot. Patients with slight distortion of the joint sometimes obtained complete relief, especially if but a few weeks had elapsed since the injury and symptoms were partially the result of initial trauma to soft tissues and prolonged immobilization. However, where distortion was extreme or arthritis present, relief was not complete and that which was obtained usually ended with cessation of treatment. Patients having a history of previous foot strain or evidence of arthritis elsewhere, other factors being equal, responded more slowly to treatment.

SURGICAL TREATMENT

Open correction of faulty union is widely practised but accurate reduction is difficult. Its usefulness is limited to the early period following fracture before osteoarthritic changes have taken place. None of the patients in this group came under our care sufficiently soon after their initial injury to warrant an open reduction.

In 1608, Fabrig performed the first astragalectomy on record for fracture of the talus. A successful result was reported. This operation is still performed by some surgeons, especially in fractures of the talus entering both ankle and subtalar joints. Sir Robert Jones stated: "Total astragalectomy is a very much overrated operation, and its functional results disappointing, even though, as Whitman insists, the foot at operation be thrust well backward on the leg; it can, perhaps, give no worse functional result than leaving a permanently crushed astragalus." The writer is of the opinion that this operation is not indicated in fractures of the talus, for in every situation subtalar triple arthrodesis or ankle fusion, or the two combined, can be used to better advantage.

Supramalleolar osteotomy may be used to correct the axis of weight bearing but does not change a deformity of the ankle mortise. In children in whom a fracture has produced a disabling deformity by disturbing growth in a portion of

Fig. 1. Six weeks after fracture passing through the medial portion of the distal tibial epiphysis and growth disc in a girl of 9 years. Anteroposterior and lateral views.

the lower tibial epiphysis, correction may be obtained and the deforming factor removed by excising the remaining portion of the epiphyseal line together with a sufficient wedge of bone to permit realinement of the tibia and ankle (Figs. 1, 2, and 3). This procedure should be accompanied by obliteration of the lower epiphyseal line of the fibula. In younger children an exeresis of the corresponding growth discs of the opposite extremity is at times indicated (8). If shortening of the limb having the fracture exists, its growth can be stimulated by drilling the metaphysis in the region of the remaining epiphyseal lines according to the method described by Ferguson.

A calcaneal tendon lengthening combined with open correction of the fracture or ankle fusion may prove advantageous, but alone serves only to correct equinus. In this series, it was performed four times in combination with an ankle fusion.

Subtalar triple arthrodesis may be required if any one of these joints be entered by the fracture. It has been performed, we believe unwisely, as a means of correcting the lateral displacement of the foot, leaving the damaged ankle joint untouched.

An ununited malleolar tip may be excised when it is a source of pain, provided its absence will not cause instability of the talus in its mortise. One patient in this series had had symptoms for 10 years from three loose bodies involving the lower third of the medial malleolus. They impinged against an osteophytic spur on the talus. Removal of the loose bodies gave complete relief, and there had been no recurrence of symptoms 20 months after operation.

By far the most useful surgical measure for a malunited fracture entering the ankle, in which osteoarthritis has manifested itself or in which disruption of the joint is so extreme that its eventual presence is inevitable, is ankle fusion. Of the 216 patients studied, there were 58 in whom the writer felt that better function could be obtained and symptoms lessened by arthrodesis. This operation was done in 24 patients, and in 22 sufficient time has elapsed to give one a fair idea of the end-result to be expected.

ANKLE ARTHRODESIS

The ankle joint was first arthrodesed by Albert, in 1878, to correct a paralytic pes equinus. The operation became widely used and met with varying success. Later it replaced resection and amputation as a surgical means of treating tuberculosis. I have been unable to discover who first used arthrodesis to eliminate disabilities caused by distortion of the ankle mortise secondary to fractures. Apparently it is an old procedure which has been used by many surgeons in many countries as a last resort for the hopelessly shattered ankle. Sir Robert Jones advocated it during the World War as a means of treating severe gunshot wounds of the ankle, painful fibrous ankylosis, and bony ankylosis in malposition. Since 1927 several references to it have been made in the literature, particularly in Great Britain. References have been in the form of a paragraph or two of generalizations with, to the writer's knowledge, no published detailed end-result study.

At least sixteen methods of arthrodesing the ankle have been described in the literature, and much is made of the difficulty of obtaining osseous union. Of the 22 cases listed in this study, definite osseous union was obtained in 21, and in the remaining case it is doubtfully present. Essentially the same procedure has been used at the New York Orthopædic Dispensary and Hospital with equal success to arthrodese a much larger series of unstable ankles resulting from anterior poliomyelitis. Previous statistics on arthrodesis for malunited fractures affecting the ankle have not been available, but Vulpius reported osseous union in 50 to 60 per cent, and firm fibrous union in 20 to 25 per cent, of his cases fused for instability due to anterior poliomyelitis.

The difficulty of securing osseous union and the danger of damaging the distal tibial epiphyseal line in performing ankle fusions before adolescence is wisely stressed by many writers, yet we do not consider youth an absolute contra-indication. We have obtained osseous union by arthrodesis in a tuberculous ankle of a child of 3 years without

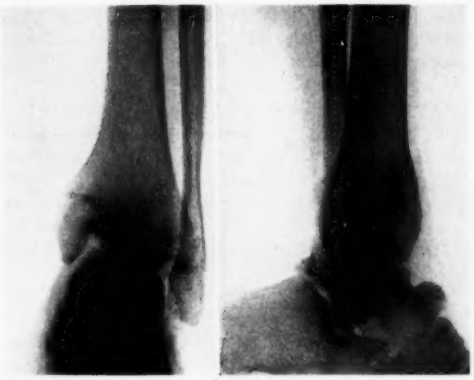


Fig. 2. Anteroposterior and lateral views of the same ankle as in Figure 1, 2 years later, showing varus deformity resulting from deficient growth of the medial portion of the distal tibial epiphysis.

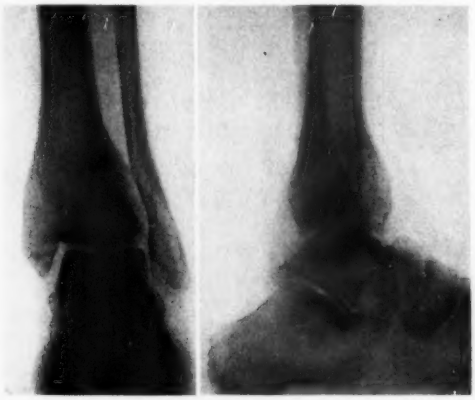


Fig. 3. Anteroposterior and lateral views of the same ankle as in Figures 2 and 3, 6 months after an exeresis of the distal tibial and fibular epiphyseal lines, together with a bone wedge sufficient to correct the deformity. Clinical result excellent. Metaphyses adjacent to other epiphyseal lines of this extremity drilled to stimulate growth. The patient is to be kept under observation and an exeresis of the corresponding epiphyseal lines of the opposite extremity done if more than one-half inch shortening results.

disturbing growth of the distal tibial epiphysis. The youngest patient in this series, aged 7, showed definite fusion in 3 months, and has been followed for 5½ years without evidence of disturbance of his epiphyseal growth due to the operation.

The degree of equinus in which an ankle is arthrodesed is of very great importance. Sir Robert Jones believed that an ankle should be fused so that the foot can dorsiflex a few more degrees than a right angle. Most writers on this subject prefer a few degrees of equinus.

In normal walking without shoes the foot is held in a calcaneal position as it is swung forward. When weight is borne upon the foot the heel does not leave the ground until the knee is well over the fore part of the foot, i.e., till the foot is dorsiflexed to considerably beyond a right angle. However, in many adults, particularly women, a contracted calf muscle prevents dorsiflexion of the foot even to a right angle, yet they may present what appears to be a normal barefoot gait except for early heel rising.

An ankle that is arthrodesed so that maximum dorsiflexion of the foot is from 100 to 90 degrees will permit an essentially normal barefoot gait. A foot in more than 10 degrees of fixed equinus gives a noticeably abnormal gait which becomes rapidly more awkward as equinus is increased until the heel either does not reach the ground or is brought to the ground by externally rotating and abducting the hip and hyperextending the knee. Not only is walking in this position difficult and awkward, but often it is accompanied by fatigue and pain through the midfoot and forefoot, due to increased strain on the tarsal joints. Tender callosities may develop under the metatarsal heads.

If one considers only walking with shoes, the ideal position for the fused joint would be such that the axis of weight bearing of the lower limb would make a right angle with a line along the surface of sole and heel of the shoe. This varies with the length of the foot, thickness of sole, and height of the heel. In the average man's shoe the foot is at an angle of 5 degrees. In a size six woman's shoe with a 2½ inch heel and ¼ inch sole it is 20 degrees. Thus maximum dorsiflexion of the foot necessary for a normal gait when wearing shoes may be less in proportion to the height of the heel. This enables those who by misfortune have a persisting equinus of more than 10 degrees to walk normally merely by proportionately increasing the height of the heel.

This does not mean that a woman who has a maximum dorsiflexion of 95 degrees is restricted to a low heel, for if the foot will allow further plantar flexion through the unfused tarsal joints to 110 degrees without strain, as it commonly will, she can have a normal gait wearing a shoe which places the foot in 20 degrees equinus. Therefore, the height of heel that can be worn is governed not by maximum dorsiflexion of the foot but by maximum plantar flexion. However, a barefoot gait is governed by maximum degree of dorsiflexion, which should be 100 to 90 degrees.

Figs. 4 and 5. Roentgenograms taken 19 months after fusion of the ankle, showing extreme dorsiflexion and plantar flexion of the foot. Approximately 45 degrees of anteroposterior motion is obtained through the unfused tarsal joints, most of it taking place through Chopart's joint. The patient was 20 years of age at the time of fusion and but little motion had been present in the ankle for several years previous to operation. The latter fact probably accounts for the excellent range of compensatory motion in the tarsal joints.

This is illustrated by the 2 following cases.

CASE 135870. Mrs. E. R.'s ankle is arthrodesed so that maximum dorsiflexion of the foot through the tarsal joints is 110 degrees and plantar flexion 125 degrees. She has a normal gait when wearing a 2½ inch heel, but without shoes has a severe protective limp, weight being borne on the metatarsal heads.

CASE 150758. Mrs. H. H.'s ankle is arthrodesed so that the foot has a maximum dorsiflexion of 95 degrees and plantar flexes to 120 degrees. When walking with or without shoes she is not conscious of any difference in the two extremities nor can one discover any abnormality in her gait.

Complete correction of the lateral displacement to a neutral position is desirable. Persisting valgus subjects the tarsal joints to abnormal weight thrusts and may cause much generalized foot pain and fatigue. Pes varus likewise disturbs the weight bearing relations of the bones of the foot, causes instability, and gives the patient a sense of insecurity of gait. Full correction of any existing rotary deformity is not so essential, but an attempt should be made to place the foot in from 0 to 15 degrees external rotation on the leg. Here again the optimum position is neutral. If the external rotation is extreme, it can be more satisfactorily corrected by an osteotomy through the proximal tibial metaphysis than through the ankle joint.

TECHNIQUE OF ANKLE ARTHRODESIS

The joint is approached by a 5 inch anterior incision in the sagittal plane dividing skin and subcutaneous tissues, and, more deeply, transverse crural and cruciate ligaments. The extensor haliucis longus and anterior tibial tendons, together with the dorsalis pedis artery, vein and deep peroneal nerve, are retracted medially, and the extensor digitorum longus laterally. The anterior lateral malleolar artery and vein are divided and ligated. The periosteum over tibial metaphysis and epiphysis with the capsule of the joint is incised and reflected until the front of the ankle is exposed as far as the malleoli. Further exposure of the articular cartilage is obtained by cutting away part of the anterior lip of the tibial epiphysis.

The articular cartilage is then entirely removed together with bone sufficient to correct the deformity. While any degree of equinus can be corrected by removal of ample bone from the tibia, it is better in severe cases to get rid of as much equinus as possible by lengthening the calcaneal tendon. With a curved osteotome opposing surfaces are "fishscaled" so as to make a soft bed of cancellous bone. Using the same incision, bone is gouged from the lower tibial metaphysis and small chips are wedged into the joint, particularly between talus and malleoli. This is important because it does away with the space created by removing cartilage and insures firm contact of bone surfaces.[1] A few bone chips are placed over the anterior aspect of the joint.

Capsule, periosteum, and other deep tissues are reunited with interrupted catgut sutures and the skin with silk.

The described method of arthrodesing the ankle must at times be modified to meet unusual situations. At some clinics, when the lateral dislocation of the talus is extreme, an incision is made just anterior to the fibula. The fibula is divided through its distal metaphysis and sunk in a groove prepared for it in the lateral aspect of the tibia. This allows complete reduction of the lateral displacement and decreases the circumference of the leg at the ankle joint.

A long leg, plaster-of-paris boot is applied with the knee in slight flexion and the foot in the desired position. Six weeks after operation the cast is removed and a short leg walking boot applied. The latter is taken off in 6 weeks. Physiotherapy is given, walking encouraged, and, if indicated, a steel arch is worn.

A STUDY OF ANKLES ARTHRODESED

The first ankle arthrodesis in this series was done January 11, 1928. The follow-up period

[1]In individuals who have had anterior poliomyelitis early in their growth period, leaving a severely paralyzed leg, the talus largely retains its fetal shape so that the talar and distal tibial articulating surfaces form arcs of unequal radii. In such cases the area of actual bone contact is small and can be increased by the procedure outlined.

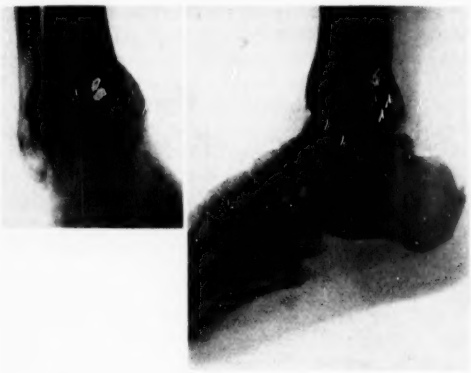


Fig. 6. Anteroposterior and lateral roentgenograms showing varus deformity and osteoarthritis of ankle, secondary to malunited bimalleolar fracture sustained 9 years previously, in a man 45 years of age.

Fig. 7. Anteroposterior and lateral views of the same ankle as in Figure 6, 5 months after ankle fusion. Osseous union present but irregular. Clinical result excellent.

ranges from 8 months to 5½ years and averages 22 months.

Of the 22 patients, 1 was 51 years of age at the time of the operation, 17 between 20 and 50, and 4 were under 20 years. They were equally divided as to sex. The end-result in the oldest patient of the series, a woman, is excellent.

The shortest time after fracture that arthrodesis of the ankle was performed was 1 month, the longest 27 years, and the average 6 years.

Nearly all patients were kept routinely 6 weeks in bed wearing a plaster-of-paris cast, followed by 6 weeks up, walking with a short leg cast on the affected extremity. All but one had osseous union demonstrated in roentgenograms at the end of 3 months, and in the average case the patient was able to return to his former occupation 4 months after operation.

Loss of motion in the ankle joint causes very little disability and is partly compensated by increased motion in the remaining joints of the foot (Figs. 4 and 5). Among adults the range of anteroposterior tarsal joint motion following ankle fusion averaged 20 degrees. It is still greater in the young. About one-half as much motion was present in those who, in addition to the ankle, had either a tarsal section or subtalar triple arthrodesis.

Most patients had 1 to 1½ inches' decrease in the circumference of the leg on the affected side as compared to the normal. This much atrophy was often present before operation, however.

Two patients had a lengthening of the calcaneal tendon, 2 had calcaneal tendon lengthening plus posterior ankle capsulotomy, 2 had a mediotarsal joint fusion, 1 a subtalar triple arthrodesis, and 1 a talonavicular arthrodesis, in addition to the ankle fusion. In the first 6, the additional operations were necessary to get rid of excessive equinus. The subtalar triple arthrodesis was done 6 years before the ankle fusion to correct an equino-varus deformity taking place in the ankle-joint itself. This partly replaced the foot under the axis of weight bearing but obviously did not restore a normal ankle joint, so that pain and disability continued. The talonavicular joint was arthrodesed because the fracture extended into it, and the talocalcaneal joint had undergone spontaneous osseous ankylosis.

RESULTS OBTAINED FALL INTO FOUR GROUPS

Group I. Excellent. A symptomless ankle. A gait essentially normal with or without shoes, so that the patient in walking is not conscious of a difference in the two lower extremities. This necessitates having the foot in 0 to 10 degrees of equinus, with a good range of tarsal joint motion and neutral lateral alinement or nearly so. Eleven of the patients are in this group.

Group II. Good. Ankle or foot symptoms mild or transitory. A gait normal with shoes but which may be abnormal without, due to excessive equinus. Seven patients fall in this group.

Group III. Fair. One who continues to have symptoms, deformity or excessive equinus yet feels better than before operation, and this subjective sense of improvement is corroborated by the physical findings. Two are in this group. In one considerable lateral displacement of the talus on the tibia remains and symptoms of foot strain are present. In the other excessive equinus has caused aching pain through the anterior portion

of the foot and tender callosities under the metatarsal heads.

Group IV. Poor. Patients not improved or worse than before operation. In this group are 2 men in whom fractures occurred 9 and 16 years, respectively, before operation. The fractures entered both ankle and subtalar joints and produced equinus-varus deformities. One had a compound infected fracture originally; the other developed infection and a pseudarthrosis following a midtarsal section to correct equinus done 12 years before the ankle fusion. In neither case has the ankle arthrodesis entirely corrected, the deformity, 20 degrees equinus and slight varus remaining in 1, and 15 degrees equinus in the other. In the former the fusion is considered solid clinically but doubtful by roentgenogram. Gait and other physical findings reveal slight improvement.

In summary, 20, or 91 per cent, of the patients are improved by, and glad they underwent, the operation. Two patients, while not worse, are not improved and are therefore dissatisfied.

When should the ankle be arthrodesed? Broomhead states: "There are two procedures alternative to immediate open correction of irreducible fracture dislocations; one depends upon the experience of the surgeon, the other upon the function which is a result of treatment by the closed method. The first alternative is to wait for about a fortnight until the swelling has been absorbed and then to fuse the ankle joint. The second alternative is to allow the patient to obtain the best result possible from conservative means and then, if the function of the ankle in 6 months or so is insufficient for his purpose, to fuse the ankle joint. As the second of these procedures is based upon the function of the foot rather than the experience of the surgeon, it is surely the sounder one to adopt. I mention the first method quite tentatively as I have no experience of it, but I suggest that in selected cases much time would be saved if such a course were followed."

DEDUCTIONS

In the light of the information gleaned from the 216 patients studied the writer is in accord with Mr. Broomhead. It is felt that any patient should have the ankle arthrodesed who at the end of 6 months still walks with a limp that is protective or mechanical in origin and in whom roentgenograms of the ankle show failure of complete reduction of the fractured fragments sufficient to account for the physical and subjective findings.

As might be expected, osteoarthritis is particularly severe and common in incompletely reduced bimalleolar fractures combined with a fracture of the posterior margin of the tibial plafond, and in compression fractures that result in disruption of the weight bearing surfaces of the joint. While the policy of waiting for function to decide is the safer, the surgeon who has had a great deal of experience in fracture dislocations and arthrodesis of the ankle should not hesitate to fuse selected cases of these types at an early date, thereby saving the patient from several months of discomfort and disability.

SUMMARY

1. Of a series of 216 fractures affecting the ankle, 88 per cent occurred in adults, and of these 71 per cent were in females.

2. Conservative measures gave partial, but seldom complete, relief from symptoms in malunited fractures affecting the ankle.

3. The most helpful conservative measure used was wearing a metal arch patterned on a plaster mold of the foot.

4. Arthrodesis of the ankle is presented as a satisfactory means of treating malunited fracture dislocations in selected cases.

5. The ideal position for an arthrodesed ankle is neutral lateral and rotary position and maximum dorsiflexion such that from 3 to 9 degrees equinus of the foot remains.

6. Of 22 patients treated by ankle fusion, 20 are improved by, and glad they have had, the operation.

REFERENCES

1. Ashhurst, Astley, P. C., and Bromer, Ralph S. Classification and mechanism of fractures of the leg bones involving the ankle. Arch. Surg., 1922, 4: 51.
2. Ashhurst, Astley P. C., and Crossan, Edward T. Prognosis and treatment of fractures of the leg and ankle. Arch. Surg., 1923, 7: 601.
3. Bick, Edgar M. History and Source Book of Orthopædic Surgery. New York: Hospital for Joint Diseases, 1933.
4. Broomhead, R. Discussion on fractures in region of ankle-joint. Proc. Roy. Soc. Med., 1932, 25: 1082.
5. Ferguson, Albert B. Surgical stimulation of bone growth, etc. J. Am. M. Ass., 1933, 100: 26.
6. Jones, Sir Robert. Orthopædic Surgery of Injuries. Vol. 1. London: Henry Frowde, 1921.
7. MacKinnon, Andrew P. Fracture of the lower articular surface of the tibia in fracture dislocation of the ankle. J. Bone & Joint Surg., 1928, 10: 352.
8. Phemister, D. B. Operative arrestment of longitudinal growth of bones in the treatment of deformities. J. Bone & Joint Surg., 1933, 15: 1.
9. Straub, George F. Arthrodesis of the ankle. Surg., Gynec. & Obst., 1927, 46: 676.
10. Trethowan, W. H. Fracture-dislocation of the Ankle-joint. The Robert Jones Birthday Volume. London: Humphrey Milford, 1928.
11. Vulpius, Oskar. Behandlung der spinalen Kinderlaehmung. 1910.

RELATION OF CHRONIC CERVICITIS TO INFECTION OF THE URINARY TRACT[1]

R. D. HERROLD, M.D., E. E. EWERT, M.D., AND H. MARYAN, M.D., CHICAGO, ILLINOIS
From the Departments of Urology and Gynecology, College of Medicine, University of Illinois

DURING the past 3½ years, we have had opportunity to study about 400 women patients with urological conditions. One year ago Ewert and Herrold reported observations on a consecutive series of 50 patients who were examined for urethral and bladder neck lesions and their relation to the disturbance of urination. We found that the treatment of the existing granular urethritis and polypoid excrescences by fulgeration, dilation, and silver nitrate relieved many of these patients of their symptoms. With the elapse of a longer follow-up period, we found some of these patients returning with a recurrence of symptoms. Clinical observation at that time suggested that in many instances the primary etiological factor was probably due to some gynecological pathology. We were further stimulated by the report of Winsbury-White in which he concluded from his experimental work that there was a direct lymphatic connection from the cervix to the urethra and floor of the bladder.

Sturmdorf (9) and others have emphasized the importance of the cervix as a chronic focus of infection for systemic disease. Moench found streptococci to be the most common bacteria present in chronic cervicitis. This was confirmed by Maryan, who found streptococci in a high percentage of infections. Also, he found by further laboratory tests that these streptococci were of the group known as enterococci, which are difficult to isolate on primary cultures, and whose outstanding characteristic is their ability to resist heat to 60 degrees C. for a longer time than other streptococci.

This series of 32 patients had some or all of a group of symptoms, the outstanding of which were frequency of urination with burning, intermittent deep pain above the pubis which was evidently at the neck of the bladder, low backache, and less frequently, radiating pains into the groin, the thigh, and upward along the course of the ureter. Many of these patients had pronounced leucorrhea.

This syndrome is frequently described as irritable bladder. Epstein and Ovtschinnikov published an article in 1931 on the pathogenesis of cystalgia in women when the urine is free from bacteria. They believe that infection is not an essential etiological factor, but rather is due to repeated circulatory disturbances in the small pelvis from menstruation, coitus, pregnancy, etc. They state that without a doubt a lasting vascular engorgement can produce chronic inflammation without the help of infection. It was our observation that bacteria may be found in every urine of patients with irritable bladder by making careful smears and cultures of the urinary sediment, although in many instances the smears do not reveal more than an occasional pus cell. Epithelial cells are more constant. Culture results in the latter part of this series yielded streptococci in a large percentage of the non-colon bacillus infections when an improved medium was used.

Twenty-nine of this series of 32 patients were followed for a sufficiently long period to permit of analysis. Coagulation of the cervix was done in each instance. A second or third coagulation was done on a few of the patients. The results as measured by relief of symptoms relative to the urinary tract are divided into two classes. The first included those in whom no improvement or but slight improvement followed coagulation of the cervix. There were 5 patients who had no improvement, and 5 who had but slight improvement. The second class included those who reported marked improvement of whom there were 11, or complete relief of whom there were 8. Therefore, it may be noted that 19 of 29 patients, or approximately two-thirds, had a satisfactory clinical response as to their urological symptoms following coagulation of the cervix. In the total series, there were 12 patients in whom the cultures revealed colon bacilluria alone or associated with other organisms, while 17 had predominant bacterial flora of mostly coccal types, usually streptococci. Further analysis indicated that 7 of the 10 non-responsive patients were those with colon bacilluria, while 14 of 19 who had satisfactory relief of symptoms were non-colon bacilluria infections. This would seem to lend support to the view that the secondary focus in the urethra and bladder is the result of continual inoculation by way of the lymphatics from the cervix, since it is well known that metastasis is much more likely to occur by streptococci as compared to colon bacilli.

In approximately two-thirds of this series cultures were also made of the cervix to compare the

[1] Read before The North Central Branch, American Urological Association, Cleveland, November 8, 1934.

growth with that from the urine sediments. In many instances like-streptococci were isolated from cultures of both areas. These streptococci are very difficult to grow on artificial medium giving small pin point colonies. While we have not made an absolute identification of the species, it seems certain that they are a member of the enterococcus group. They do not produce hemolysis or greening of the blood agar when first isolated, and would be termed indifferent streptococci as regards their reaction on blood agar. Direct smears as a rule, reveal pleomorphic forms, often more gram negative than gram positive. Cultures were made of the cervix of 10 colon bacilluria patients. Seven yielded no colon bacilli from the cervix, 2 but two or three colonies, and in 1 instance only, there was a predominant growth of colon bacilli. This observation would seem to indicate that like flora of the cervix and urine, sediment was not dependent at the time of culture on recent inoculation of each other by way of the vagina or urethra.

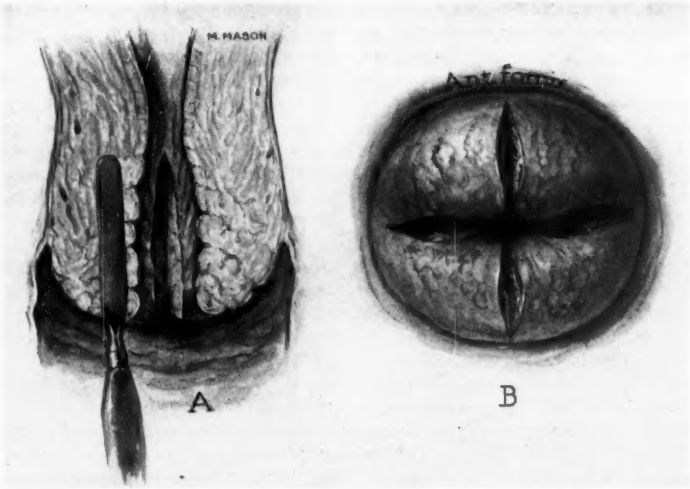
CHRONIC CERVICITIS

The base of the bladder is intimately connected below to the anterior surface of the supravaginal portion of the cervix and above as far as the area of the internal os. This area is the anterior part of the base of the broad ligament or parametrium, which is known as the cardinal ligament of the uterus, and is its main support. In this area, between the peritoneum and the pelvic fascia, is incorporated the uteropubic ligament, an abundance of loose areolar connective tissue, smooth muscle fibers, a rich network of lymphatics, and blood supply. This is the weak spot that is stretched or ruptured during parturition and later contributes to the development of cystocele. Normally its depth measures about one-third of an inch. It is logical to assume that such intimate histo-anatomical relationship would enable chronic cervicitis to be a factor in the production of an irritable bladder, either by direct extension or most likely through the lymphatics. This histo-anatomical lymphatic relationship is not brought out in the various textbooks dealing with the anatomy and lymphatics of the bladder and cervix of the uterus. Winsbury-White has fully demonstrated, experimentally, by injection of India ink as well as living and dead tubercle bacilli into the cervices of guinea pigs and rabbits, that not only is there lymphatic connection between the bladder and the cervix, but also between the cervix and vagina. In chronic cervicitis there is also a perivascular lymphocytic infiltration, and a paracervical parametritis.

It is accepted among gynecologists that chronic cervicitis is due to a persistent infection in the depths of the compound racemose glands, which is characterized pathologically by a periglandular round cell infiltration. The cervix is prone to infection because of its situation in the vagina and because it is lacerated during labor. The crypts and lacunæ of the mucous membrane afford a protection for the invading organisms, and in these areas the gonococci and other bacteria may lie dormant for long periods of time.

Investigators agree on the bacterial flora of the surface of the pathological cervical canal, but no mention has been made of the bacterial flora in the depths of the glands. Maryan, after grinding under aseptic technique the cervical tissue which was enucleated equally by Sturmdorf's (10) method and conization with the high frequency cutting current scalpel, isolated the heat resistant enterococcus from the depths of the compound racemose glands in 80.4 per cent of the patients. He has shown bacteriologically and pathologically that chronic cervicitis is a deep infection of the compound racemose glands, which is characterized by a periglandular round cell infiltration, and by a perivascular lymphatic lymphocytic infiltration of the deep connective tissue stroma or musculature. Therefore, it can be seen that the glandular structure of the compound racemose glands encountered in the stratified squamous epithelium of the portio-vaginalis portion of the cervix (the vaginal portion of the cervix which is normally free from glands), is due to an extension of the proliferation of the normally present compound endocervical racemose glands. This extension of the proliferation is referred to in the literature as an erosion, a term which of course is a misnomer as it is not a substitution of the stratified squamous epithelium by the cylindrical epithelium of the endocervix primarily, but a downward displacement of the compound racemose glands, with its associated inflammation and regeneration. Rightfully it should be called chronic pan cervicitis or chronic cervicitis, as the entire cervix is invaded. Therefore, with this understanding of the pathological genesis of chronic cervicitis, one is enabled to treat cervical lesions adequately. Macroscopically "erosion" or chronic cervicitis is evidenced by redness of varying degrees of the cervical lips surrounding the patulous external os, together with an abundance of mucopurulent secretion from the cervical canal. It has been customary to classify these changes under the following clinical divisions:

1. Congenital erosion—This lesion is encountered in virgins or young girls.



Spatula tip *in situ* indicating that contact is made against the edge of the blade. Figure at right shows the depth of the linear striping of the cervical canal.

2. Ectropion or eversion of the cervical lips, which is truly not an erosion but a velvety red bulging forward of the endocervical mucous membrane breaking through the mucocutaneous junction, normally situated inside the external os.

3. Simple erosion, which is a replacement of the stratified squamous epithelium of the cervical lips by the high cylindrical epithelium.

4. Follicular erosion, which is characterized by the presence of retention cysts, the so called Nabothian follicles or cysts.

5. Papillary erosion, and it is manifested grossly by velvety red elevations on the surface of the cervical lips.

6. The healing of erosions, or replacement of the glandular misplaced epithelium with stratified squamous epithelium.

These terms may be conveniently retained as long as we bear in mind that they represent only progressive grades in the same pathological process of chronic cervicitis.

TECHNIQUE OF COAGULATION

The heavy mucoid discharge from the cervix is dissolved and removed with caroid powder, which dries the canal and makes its surface more visible. No local anesthesia is used in the cervix. A tenaculum is not used to hold the cervix in place for the reason that adequate exposure may be obtained with Guttman's operative speculum. Coagulation is done preferably between the fifth and the fifteenth day after menstruation since complications are less likely to follow if carried out at this time.

Other lesions of the cervix should be ruled out before coagulation, such as syphilis, tuberculosis, early carcinoma and pin point leucoplacias. Because of the rich supply of lymphatics capable of producing such associated lesions as metritis, parametritis, and uterosacral cellulitis, it is advisable also to rule out any chronic inflammatory residual pelvic pathology. Coagulation of the cervix should never be done in the presence of an acute or subacute inflammatory lesion of the internal or external generative organs.

The short circuit method of diathermy coagulation was used with the indifferent tin plate electrode under the patient. The spatula tip (3 centimeters long by 3 millimeters wide) positive electrode (Fig. 1), was used for coagulation of the cervix. The proper dosage with the universal Bovie machine is obtained by setting the indicator on 40 of the coagulation meter scale which gives the proper milliamperage.

Where the cervix has an edematous and acutely inflamed appearance associated with marked lacerations, it is best to treat it first by topical applications of 10 per cent tannic acid and glycerin into the cervical canal, supplemented by daily hot douches. This will shrink the cervix materially and reduce the activity of the chronic inflammatory process.

We have employed routinely the linear striping of the cervix commencing within the internal os, extending to the external os, and continuing this linear striping on the cervical lips, at right angles to the linear striping of the cervical canal (Fig. 1). The edge of the spatula tip electrode was found most suitable. The tip is first placed firmly against the cervical tissue, and then coagulation is begun. The coagulation of the cervix was usually completed in one sitting. The amount of coagulation should be sufficient to reach beyond the gland bearing tissue and into the adjacent stroma. In this way, sufficient destruction of the infected gland bearing tissue will be produced, as well as adequate drainage.

Usually the crucial incisions were made at 12, 3, 6, and 9 o'clock for hypertrophic eroded cervices with bilateral lacerations. In some instances with marked hypertrophy of the upper lip, additional linear striping was done at 11 and 1 o'clock. However, one must individualize the extent of coagulation in different patients. The failures that occur following coagulation or cervical plastics are usually due, as shown microscopically by Koster and by Wolfe, to remnants of the uppermost infected gland bearing tissue near the internal os. Further coagulation, if necessary, is done after 3 weeks, since the height of the tissue reaction has subsided by this time. Fractional coagulation is preferable for chronic gonorrheal infections and in general office practice.

A few patients complain of mild to severe cramp-like menstrual pains during coagulation, but as a rule they are transitory. Patients are instructed to abstain from the use of douches during the postcoagulation period. Close postoperative observation is given with cleansing of the wound as indicated. Epithelization is usually complete between the fourth and sixth weeks.

Three possible complications may follow coagulation of the cervix, namely: hemorrhage, stenosis, and pelvic infection. Bleeding during the days immediately following cervical coagulation is usually benign and due to the oozing of the sloughing surface. Very infrequently severe secondary hemorrhage is encountered about the twelfth to the fourteenth day as a result of too extensive coagulation. There will be a slough beyond the area of coagulation because of the deep penetration of the generated heat. On this account, severe secondary hemorrhage may occur from sloughing of the cervical branch of the uterine artery in the region of the internal os where coagulation has been too extensive. Stenosis is avoided by follow-up dilatation of the cervical canal as employed by Curtis.

RECAPITULATION

While this work was in progress a personal communication was received from Dr. J. Howard Shane regarding unpublished work which he has done in co-operation with a gynecologist, Dr. Mahon. Their results parallel ours very closely as regards clinical proof that adequate treatment of chronic cervicitis is followed by relief of many of the so called "irritable bladders." They believe that cauterization of the cervix does not give the greatest benefit unless follow-up treatments are given for several weeks. Their postcauterization management consists of dilatation of the cervical canal, and application of silver nitrate to the cervix, both internally, and externally, at intervals of one week. Certainly, as we have emphasized, dilatation of the cervical canal is an important follow-up measure.

As mentioned, our clinical results indicate that treatment of the cervix as described gives satisfactory relief of symptoms referable to the urinary tract in approximately two-thirds of the patients. As yet our investigation has not proved the exact mechanics of such improvement. We lean to the view that constant reinfection of the urethra and bladder, particularly with enterococci, is an important contributing factor. In many instances, clinical improvement has been coincident with a decrease of the bacterial flora of the urinary tract. On the other hand, some patients with improvement have continued to yield enterococci from cultures of the urinary sediment. It is possible that such remaining infection is more superficial than before cervical coagulation, and would disappear spontaneously or by treatment after a longer period had elapsed. Further investigation is required before the exact mechanics of improvement can be established.

It has been emphasized by others that the cervix frequently is a focus of systemic infection, particularly arthritis and iritis. One arthritic patient in our series was relieved of all symptoms within 4 weeks after coagulation of the cervix.

There were 2 patients in our series who had symptoms similar to a group that is frequently described as idiopathic fever. Kintner and Rowntree, in an analysis of 100 cases of long continued low grade idiopathic fever, state that females constitute almost three-fourths of their entire group. A diagnosis of tuberculosis had been made in both of these patients and one had been sent to a sanatorium in New Mexico where, after several weeks of observation, it was decided that she was not tuberculous. After coagulation of the cervix in this patient the temperature returned to normal and the urine cultures no longer yielded

streptococci. The second patient continued to have fever after coagulation but streptococci persisted in the urine cultures and it is possible that all of the infected gland bearing tissue was not destroyed. In such instances the Sturmdorf operation would seem preferable.

It is well known that the incidence of interstitial cystitis is higher in women than in men. One patient of our series with an early interstitial cystitis had definite improvement following coagulation of the cervix. A further study is being made to determine a more exact relationship between infection of the cervix and this type of cystitis.

SUMMARY

In a series of 32 patients with irritable bladder, there was complete relief or marked improvement in two-thirds of the series following coagulation of the cervix.

Improvement occurred more frequently in patients with streptococcus infection as compared to those with colon bacilluria. Most of these patients had macroscopically clear urines and the sediment revealed bacteria with but few or no pus cells. The heat resistant so called enterococcus group was the most common type of streptococcus isolated in the examination and study of the urine sediments.

The infected gland bearing tissue of the cervix was destroyed by deep crucial incisions. It is necessary that coagulation be followed by dilatation of the cervical canal including the internal os.

BIBLIOGRAPHY

1. Curtis, A. H. J. Am. M. Ass., 1932, 98: 861.
2. Epstein, I., and Ovtschinnikov, N. Ztschr. f. urol. Chir., 1931, 31: 231.
3. Ewert, E. E., and Herrold, R. D. Illinois M. J., 1934, May.
4. Kintner, A. R., and Rowntree, L. G. J. Am. M. Ass., 1934, 102: 889.
5. Koster. Surg., Gynec. & Obst., 1920, 31: 310.
6. Maryan, H. O. Am. J. Obst. & Gynec., 1932, 23: 555.
7. Moench, L. J. Lab. & Clin., 1934, 9: 289.
8. Shane, J. H. Personal communication.
9. Sturmdorf, A. Surg., Gynec. & Obst., 1916, 22: 93.
10. Idem. Gyno-Plastic Technology. Philadelphia: F. A. Davis Co., 1919.
11. Winsbury-White, H. P. Brit. J. Urol., 1933, 5: 249.
12. Wolfe, S. A. Am. J. Obst. & Gynec., 1932, 24: 87.

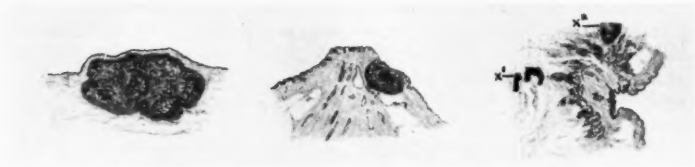


Fig. 1. Fig. 3. Fig. 5.

Fig. 1. First recurrence in scar, right side. Reduced 1/6.
Fig. 3. Metastatic nodule, left breast. Reduced 1/6.
Fig. 5. Tumor, left axilla, skin, nodes, *x*. Reduced 1/6.

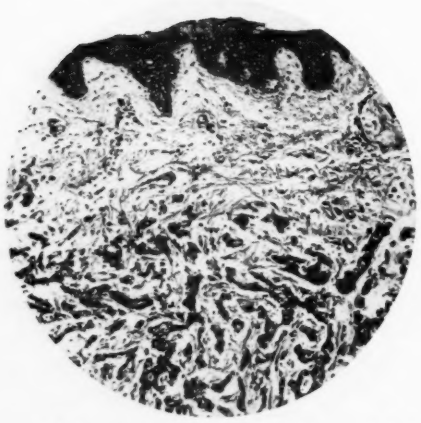


Fig. 2. Scirrhous carcinoma, peripheral area of first recurrence, Figure 1. × 70.

Fig. 4. Nodule of scirrhous carcinoma, metastatic in left nipple. (cf. Figure 3.) × 70.

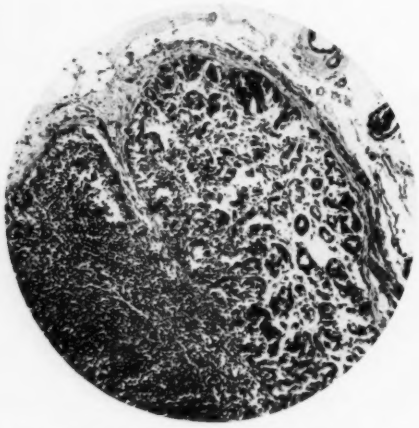


Fig. 6. Lymph node left axilla with malignant invasion cf. Fig. 5, *x'*.) × 70.

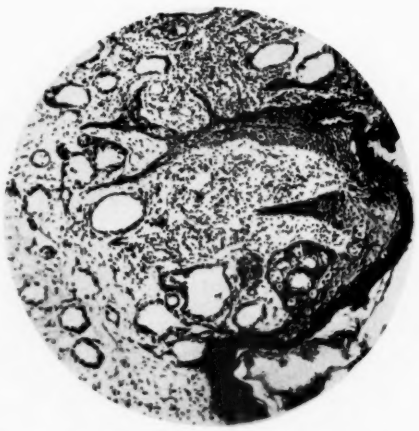


Fig. 7. Skin of left axilla (irradiated) with Paget-like changes and malignant cysts. (cf. Fig. 5.) × 70.

CARCINOMA OF THE BREAST

Survival for 24 Years with Local Recurrences and Metastases in the Opposite Breast and Axilla

M. C. TOD, F.R.C.S., and E. K. DAWSON,[1] M.B., Edinburgh, Scotland
From the Laboratory of the Royal College of Physicians, Edinburgh

ALTHOUGH the survival for many years of patients who have been subjected to radical operation for carcinoma of the breast is comparatively common, the successful treatment of a metastatic growth in the opposite breast and secondary invasion of lymph nodes in the opposite axilla appears to be sufficiently rare to warrant the publication of the case.

In 1910 the patient, a married female aged 47 years, primipara, was admitted to the Edinburgh Hospital for Women and Children, where Dr. Elsie Inglis performed a radical operation for scirrhous carcinoma of the right breast. The pectoral muscles were removed and the axilla cleared.

In 1921, the patient, aged 58 years, was re-admitted to undergo an operation for uterine prolapse. The menopause had been complete since the age of 50 and her health had been excellent. On examination, the operation scar was noted to be sound and healthy except for a small scab at the lower end which had persisted since the operation.

In 1922, she reported with a small lump at the lower end of the scar noticed 10 days previously and increasing in size with redness of the skin. Examination showed a hard lump the size of a florin, disc-shaped and lying in the thin tissue over the fifth intercostal space. It was movable on the chest wall, but the overlying skin was fixed, red and glazed. One and one-half inches lateral to it was a second nodule the size of a pea.

At operation both nodules were removed with a sufficient ellipse of skin and subcutaneous fat. Histological examination revealed that the nodules showed scirrhous carcinoma with tumor cells present near the skin margins (Fig 1, the larger nodule, and Fig. 2).

In 1931, the patient reported with a swelling in the left (opposite) axilla, present for 12 months and gradually increasing in size, with occasional ulceration and the discharge of an offensive yellow fluid. Examination showed a small mass in the left axilla which appeared to consist of several lymph nodes matted together, about the size of a golf ball and adherent to the underlying tissues. The skin overlying was inflamed and fixed, and serous fluid exuded on pressure. At the same time, the scar on the right side showed three separate, flat, reddish nodules fixed to the underlying tissues about the midclavicular line. No clinical lesion was found at this time in the left breast. The left axilla was treated by one of us (M.C.T.) with 100 milligrams of radium at 2 centimeters and the three nodules in the original scar with 25 milligrams at 1 centimeter on surface applicators, each application delivering one skin erythema dose (600,000 ergs per cubic centimeter).

Three months later there was still a tumor the size of a walnut in the left axilla; it was scabbed and still fixed to the skin but was now movable over the deeper tissues. The left nipple now showed a slightly reddened area on its lateral aspect and was scaly; on palpation, the discolored area felt thickened. The thickened area in the left breast was excised locally, with the nipple (Figs. 3 and 4). The nodes in the left axilla with the surrounding fat and the overlying skin were dissected away (Figs. 5–7).

Since this last treatment early in 1931, the patient has remained under supervision and has been very well. She was employed as a cook in an Institution since the first operation in 1910 until 1933, when she regretfully retired on her old age pension.

She was examined and photographed in September, 1934 (Fig. 8). At the age of 71, she feels well and able to do her own housework and to help to nurse an invalid. The scar of the primary operation (right side) shows an area of very dark pigmentation with some hyperkeratosis, but no sign of active disease. The left breast shows a linear scar in place of the nipple but is soft, movable, and appears normal for a woman of this age. There is a scar in the left axilla but it is perfectly movable and there are no palpable nodes. No nodes are palpable in either supraclavicular region. There is no cough, no shortness of breath, no swelling of the abdomen. Sometimes she feels a little stiff but has no pain anywhere.

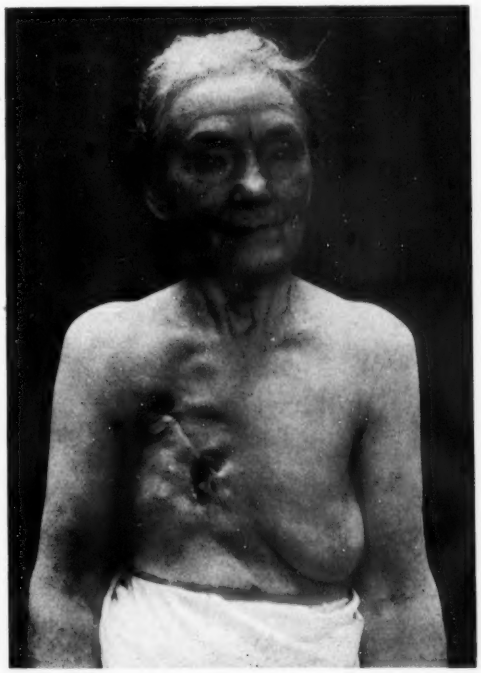


Fig. 8. The patient in September, 1934, aged 71 years, 24 years after primary radical operation (the darkened area in the scar is largely pigmentation).

[1] Carnegie Research Fellow.

Histology of the different areas examined. The original operation tissue is not available. The first recurrence in the scar shows glandular carcinoma, a typical scirrhous growth (Fig. 2). The nodule from the left breast shows a similar histological structure (Fig. 4) though somewhat more cellular. In our opinion, the position of the nodule (Fig. 3), the nature of the growth, and the absence of involvement of the mammary gland tissue suggests a metastatic tumor rather than a new and independent neoplasm in this opposite breast. The axillary tissue on this side shows malignant infiltration reaching to the skin and two small nodes invaded by cancer cells (Figs. 5, at *x*, 6, and 7). The cells are active in spite of irradiation. The Paget-like changes in the axillary skin and the small cystic areas with partially necrotic tumor cells may be due to radium treatment (Fig. 7). This left axillary area of carcinoma may be an independent metastasis but, more probably, is a secondary spread from the skin nodule in the left nipple, though the latter became evident clinically at a later stage.

It is not suggested that there is any special interest in the method of treatment, which merely followed the manifestations of the disease. The unusual feature is the extraordinary degree of resistance shown by this patient to the malignant growth. The survival is not exceptional. At the Clinical Congress of the American College of Surgeons in 1932, where special emphasis was laid on the curability of cancer, Wainwright reported 3 cases well and apparently cancer free for over 20 years, though none showed recurrence or metastasis; Guthrie reported 1 case well for 16 years and McLean 9 cases well for 15 to 25 years Pfahler and Parry[1] reported 22 cases alive 20 to 22 years after treatment; 6 of these had recurrences treated, none had metastases. Our patient had malignant tumors of the opposite breast and axilla which, from the clinical course and result of treatment, we consider are probably metastatic; a primary growth in the second breast and axilla is unlikely to have remained clinically cured for nearly 4 years after local excision of superficial nodules. The mode of involvement of the second breast is obscure in the absence of any clinical evidence of spread across the sternum.

[1]Ann. Surg., 1931, 93: 412.

SYPHILIS OF THE BLADDER

EDWARD O. FINESTONE, M.D., NEW YORK, NEW YORK
From the Service of Dr. Edwin Beer at the Mt. Sinai Hospital

IN reviewing the literature on syphilis of the bladder, one is struck with the laxity with which cases are reported. The controversies regarding its rarity depend entirely upon the criteria used in diagnosis, and not upon the power of observation or diagnostic acumen of the contributors. As yet, not one case reported has measured up to the standard set by Young, who maintains that the diagnosis cannot be categorically proved unless the treponemata be demonstrated in the lesions.

INCIDENCE

The incidence varies strikingly with the observer. Chocholka (2), who seems to be the most prolific contributor, added 6 more cases in 1931 to 56 others he had seen since 1911. In 1923 (3) he reported 14 cases from his own practice, 18 cases collected from a series of 105 cystoscopies at the clinic at Prague, and 13 observations of parasyphilis; and in 1928 (4) he added 11 new cases, making a total of 56 cases. Chocholka stated that in 1900 the literature contained only 14 cases, whereas in 1925 he was able to collect 169 cases. The writer has collected a series of 158 cases which have been analyzed. The discrepancy between this number and that of Chocholka arises from the fact that no cases are included prior to 1900. Thirty-nine cases of Chocholka (5) reported in 1926 and 30 cases of Duvergey are not included nor are the several cases in unobtainable foreign periodicals. Valverde (1932) reports that of 201 patients complaining of vesical symptoms, upon whom 282 cystoscopies were performed, 57 were diagnosed and treated as vesical syphilis. Raurich (1930), in a series of 53 routine cystoscopies upon cases of lues, found 4 with evident bladder manifestations which were diagnosed as vesical syphilis. Young is very skeptical about the cases reported, not having seen any himself; and Levy and Zimmerman, who undertook to determine the incidence, found no lesions in 25 cases of secondary syphilis examined cystoscopically. The rarity of syphilis of the bladder is attested by such pathologists as Kaufman, Aschoff, and MacCollum, who either do not mention it or refer to it through the medium of cases reported in literature. Evidently, none of these pathologists has personally seen a case or examined a specimen. Stokes states that "between 1916 and 1924 no undoubted case was observed at the Mayo Clinic." In the past 25 years neither Dr. Beer nor any of his assistants on the Urological Service at the Mt. Sinai Hospital has observed a case of syphilis of the bladder.

There is no reason to believe that syphilis of the bladder does not exist. The spirochæta has invaded every tissue of the human body, but its demonstration has been rendered especially difficult in epithelium lined structures as the lung, stomach, and bladder.

PATHOLOGY

In spite of the number of cases reported, only a few observers have investigated the histopathology. Denslow (1918) is credited as being the first to make a diagnosis of syphilis of the bladder on the basis of the histopathology. On suprapubic cystotomy, he curetted lesions which were examined and reported to him as syphilitic condyloma. Unfortunately, he does not give a detailed description of the histopathology in his case report. The case reported by Danforth and Corbus was also operated upon and the pathology reported by Dennie as follows: "The lesion is seen to consist of two parts—an upper dense, finely striated portion about 4 millimeters thick and a lower narrow core. Microscopically, the former shows many slender epithelial fingers connected above by thin bridges and below penetrating the corium." Although Pugh reports that he found typical syphilitic histopathology in the tissue of one case and a suggestive histology in another, a detailed description is not available. Valverde describes the histopathology on his first case as follows: "Hyperplasia of endothelial cells with slight infiltration of mononuclear cells of chronic inflammation, lymphocytes, and plasma cells. Cystic cavity in center with degenerating cells. One part was homogeneous (without structure) showing necrosis. The second case showed chronic inflammation with hyperplasia of the epithelial lining, one section showing a tendency to anaplasia. In the chorion there was an infiltration of the cells of chronic inflammation."

Only eight contributors (Graff, Denslow, Saelhof, DeGouvea, Danforth and Corbus, Pugh, Valverde, and Levy and Tripoli) have subjected the lesions to microscopic study. Only the case of Levy and Tripoli presents typical syphilitic

histopathology, the photomicrographs showing endarteritis with thrombosis, perivascular lymphocytic infiltration, occasional multinucleated giant cells and small areas of necrosis. The specimens were removed from the bladder at autopsy, but the photomicrographs do not show the relation of the syphilitic changes to bladder mucosa. Furthermore, the bladder was entered accidently during the operation and a fistula resulted from the attempt to dissect the gummatous mass from the outer wall of the bladder. Of the other cases reported in detail, not one presents a specific pathological picture which could be diagnosed as syphilis. However, it has been argued that the lesions closely resemble those of condyloma lata. McCarthy describes the histopathology of condyloma lata as follows: "The epithelium undergoes gigantic acanthosis, the suprapapillary portion is greatly hypertrophied and the interpapillary rete cones are enormously elongated and drawn out. The latter often grow in an irregular fashion producing lateral branching or "daughter" processes. The whole epithelium is saturated with edema to a marked degree and the cells appear larger than normal, due to this absorption of fluid. This type of lesion offers a beautiful example of intracellular and intercellular edema. For the most part the cells stain badly or not at all. The intercellular spaces are dilated, and wandering leucocytes can be seen making their way through the epithelium. In well developed lesions these cells unite to form small collections, causing dissolution of cellular structure and thus producing small abscesses. The infiltrate has a uniform density in the papillary bodies, while it forms a thick mantle about the vessels of the subpapillary and lower layers of the cutis."

This description corresponds rather closely with the histopathology of the cases reported by Danforth and Cobus, Valverde, and the case reported by myself, although the last is certainly not a proved case. It is argued that if there is nothing specifically characteristic in the pathology of condyloma lata, there is no reason to expect that the pathology of bladder syphilis should be characteristic. The combination of a mucous surface, irritation and syphilis is known to produce the lesions characteristic of syphilitic condyloma which are commonly found about the anus. There is no difficulty in establishing their identity, since they are teeming with treponemas, but this difficulty has not yet been surmounted in the case of bladder syphilis. Here, the same combination of factors exists and the lesions are, therefore, presumed to resemble condyloma lata histologically.

SIGNS AND SYMPTOMS

Grossly, a variety of lesions have been described on cystoscopic observation. These seem to depend upon the stage of syphilis and the duration of the illness. Although some writers claim that the lesions are sufficiently characteristic to make a diagnosis, others state that they resemble the lesions of tuberculosis, malignancy, papillomata, and bilharziasis. Although some of the lesions, especially the villous vegetating growths and the papules appear to present a typical cystoscopic picture, the writer will not attempt to go into the description of the various lesions seen, since he does not believe that these help in the diagnosis.

The symptoms are those of any vesical irritation, namely: frequency, dysuria, tenesmus, depending upon the reduction in the bladder capacity, and at times hematuria.

Cystoscopically, the lesions reported have varied from the appearance of a simple cystitis to the most extreme pictures of tumor with ulceration. Most frequently, the lesions are situated on the trigone, about the ureteral orifices and sphincter.

DIAGNOSIS

The case that would receive preference in the diagnosis would present the following factors: (1) A previous history suggesting syphilis; (2) the presence of active syphilis in the form of a generalized rash, mucous membrane lesions, adenopathy, gummata, or ulcers elsewhere; (3) a positive Wassermann; (4) the absence of all other etiological factors; (5) a rapid amelioration of the symptoms with disappearance of the lesions as shown by cystoscopic control following the institution of antiluetic treatment.

The chief discussion of all cases of bladder syphilis revolves about the criteria used in making the diagnosis. If any one of the factors mentioned be taken by itself, it could be easily eliminated as substantial proof of the diagnosis. We must revert to the finding of the spirochæta as the only method for categorically proving any case. In view of the fact that the spirochæta has never been found either in the lesions or in the sedimented urine, we must discard all the cases reported or select a few which offer the maximum of corroborative clinical findings.

Assuming that a hypothetical case presents the signs of activity, a positive blood Wassermann, and responds rapidly to treatment, we cannot very well discard it in spite of the absence of spirochætæ or distinctive pathology. It has been shown that stomach syphilis presents no uniform or distinct syphilitic pathology. It is hoped that

further study will decide the actual histopathology of syphilis of the bladder by concomitant finding of the spirochæta.

Then, only, may the non-specificity of the histopathology be established and eliminated as one of the required factors.

Chocholka and Valverde have entered into a controversy over the relative merits of the cystoscopic appearance and the response to treatment as guides to diagnosis. Obviously, the latter is the more important. However, we know that the arsenicals and mercury, especially when given intravenously, are excellent remedies for ordinary coccal or bacillary infections of the genito-urinary tract. The manner in which neoarsphenamine produces a cure is not well understood. Friedman showed that it decomposes into formaldehyde, but he rated this quantity as only .000004 per cent. If this amount were effective, cures should be expected with much larger doses of urotropin, which has been ineffective in ordinary coccal infections and in cases reported as syphilis of the bladder.

The strength of the argument for the therapeutic test has been increased by the results obtained by the use of bismuth alone in the antiluetic treatment.

PROGNOSIS

If a case is established as one of syphilis of the bladder by the therapeutic test, it follows that the prognosis must be uniformly good. Most of the observers have based their case reports upon the rapid response to treatment which has been striking. A few cases of recurrence of symptoms and lesions have been reported. Correa cites 3 cases observed between 1923 and 1929. Each one was originally diagnosed as syphilis of the bladder by cystoscopic findings and the response to treatment. When they recurred, they again responded to antiluetic treatment. In the series of 158 cases reported here, 5 cases showed evidence of recurrence. Only 1 was definitely cured; 2 were reported still under treatment; 1 died, and the other was not controlled.

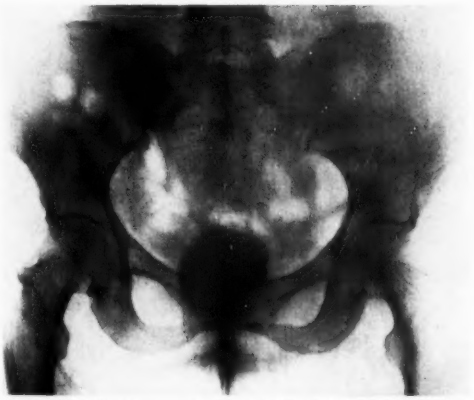


Fig. 1. Cystogram of Case 1 (B. L.) taken May 25, 1928, at the time the patient was suffering intense dysuria and tenesmus. The great diminution in bladder capacity and the expulsive effort are responsible for the reduplication and the small size. On the left lateral wall is seen the filling defect corresponding to the vegetating growth observed cystoscopically.

Case 1. B. L., married, female, aged 55 years, gave a history of having been treated for a gonorrheal infection about 1 year prior to her admission to the X Hospital. While she was treated for the gonorrheal infection she had no urinary symptoms. Beginning about January, 1928, she began to have marked frequency of urination, dysuria, and incontinence. She was admitted to the X Hospital on February 21, 1928, and discharged March 9, 1928. Cystoscopy showed a marked congestion of the entire bladder wall, more marked around the trigone with necrotic areas in that region. There was marked bullous edema. The ureteral orifices were normal. The sphincter margins were markedly congested. X-ray examination of the genito-urinary tract showed a small calcific shadow, the size of a split pea at approximately the left ureterovesical orifice. The kidneys were normal in size, shape, and position. The urine contained many pus cells in clumps. The blood chemistry showed non-protein nitrogen, 30 milligrams; urea, 14 milligrams; uric acid, 2.3 milligrams, and sugar, 91.0 milligrams. The blood Wassermann was negative. The blood pressure was 175/85. The blood count showed red blood cells 3,900,000; hemoglobin, 70 per cent; white blood cells, 9,400; with 72 per cent polynuclears and 28 per cent lymphocytes. She was discharged from the hospital with a diagnosis of hypertension and chronic cystitis.

She was admitted to Y Hospital on May 5, 1928. The complaints were the same as on admission to X Hospital. She was found not to be acutely ill. The right pupil was greater than the left and reacted sluggishly to light. The skin showed a maculopapular rash involving the face, trunk, and extremities. This was diagnosed as a papular eczema on May 7 by the dermatologists, but on May 9, 1928, the blood Wassermann was reported 4+ and on May 14 the diagnosis of the skin condition was changed to a secondary syphilide. On May 7, the urine showed specific gravity of 1010; acid reaction, trace of albumin, some epithelial and white blood cells.

On the same day, urea nitrogen was 21.8 milligrams and sugar 112 milligrams. On May 10, 1928, mixed treatment consisting of 1 dram of the mercury and iodide mixture was administered three times daily. Bladder irrigations with 1:5000 acriflavine were given twice daily beginning on May 15 and 15 minims of tincture of hyoscyamus was given three times a day beginning May 10. In spite of this treatment, the patient still presented the same symptoms with intense dysuria and frequency so that she voided every half hour during the day and four or five times during the night. On May 22, 1928, she was subjected to a cystoscopic examination by the writer and a marked diminution in bladder capacity was noted. The region of the left ureter, the left lateral wall of the bladder and the trigone on the left side, extending down to the sphincter, was a site of a vegetating growth. The lesions were villus-like, yellowish pink, translucent, and sprang

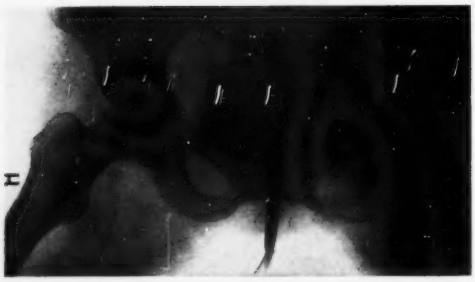


Fig. 2. Cystoscopic appearance of "vegetating syphiloma" described by Corbus and Danforth (Case 52 in chart) believed by many observers to be typical of bladder syphilis.

directly from the floor of the bladder. There was no pedicle or frond-like appearance. There was bullous edema toward the sphincter. The right ureter orifice was normal and the left ureter orifice could not be seen because of the vegetating growth. Bladder urine was cultured and showed only a few colonies of Staphyloccus albus and the guinea pig inoculated with bladder urine showed no evidence of tuberculosis. Smears of the centrifuged sediment revealed no tubercle bacilli.

A cystogram made on May 28, 1928, showed the great reduction in the bladder capacity which was evidenced by the patient's symptoms. The patient was unable to retain more than 1 to 2 ounces of the opaque material, so that an adequate visualization could not be obtained. But the left lateral wall of the contracted bladder revealed an irregularity which corresponded to the distribution of the lesion seen through the cystoscope. The patient was given antiluetic treatment in the form of neoarsphenamine 0.45 grams on May 19, May 22, and June 5, and an injection of bismuth on May 29.

The original blood Wassermann, which was 4+ on May 9, became negative on May 28 and again 4+ on June 4, 1928. Under antiluetic treatment there was a marked and rapid amelioration of the bladder symptoms so that on May 24 there was only very slight dysuria and the patient was voiding every hour or two throughout the day instead of every half hour and only three times at night. On May 24, the skin rash had faded considerably.

On May 26, 1928, a second cystoscopy was performed by the writer, and specimens were removed from the villous masses by means of an operating forceps. Unfortunately, a Levaditi stain could not be made because the specimens were immediately placed in formalin. The histopathology showed a marked proliferation of the epithelial lining with projections above the level of the bladder mucosa and gland-like inclusions of epithelial elements. There was moderate edema with round cell infiltration. There was no typical endarteritis, peri-vascular infiltration, or areas of focal necrosis. The interpretation by Dr. Paul Klemperer was "cystitis glandularis."

Following the patient's discharge from the hospital, antiluetic treatment was continued by means of the injections of neoarsphenamine 0.45 grams twice weekly so that she had had eight injections up to July 25, 1928, and two injections of mercury salicylate and five of oxycyanide of mercury. On this date, there was a marked improvement in her general condition. She looked well, had gained weight, and there was no skin rash. There was no frequency or urgency and no burning on urination. She voided only three or four times during the day and twice at night. The urine was entirely clear. Cystoscopy on July 25, 1928, showed several small, irregular elevations about the left ureter orifice. These excresences were much smaller than those seen on primary cystoscopy and were localized above the left ureter orifice only. The trigone and right ureter orifice were normal in appearance. The bladder capacity was normal.

Specimens were again removed for biopsy and these were reported as showing also a cystitis glandularis but the later specimen showed more edema and round cell infiltration and foci of large swollen endothelial cells (foam cells) and foci of necrosis.

The patient was again seen on December 6, 1928, at which time she made absolutely no complaints. There were no bladder symptoms and she was still receiving neoarsphenamine and mercury every week with the exception of one month rest. The blood Wassermann taken about November 1 was 2+.

On April 13, 1929, there were absolutely no urinary symptoms and the urine was crystal clear. Cystoscopy revealed the bladder to be entirely normal. Cystogram made on this date showed a perfectly normal bladder with normal capacity.

Up to this point, a review of the case would leave one with the impression that he were dealing with a well established case of syphilis of the bladder. Had the case been reported in 1929 and not followed until the end of 1931, this error would undoubtedly have been made.

The patient was not seen again until the spring of 1931, when she again complained of frequency, dysuria, and tenesmus. She was not examined but referred to the Mt. Sinai Hospital for further study. However, she was not admitted immediately, and thereupon made the rounds of several hospitals where diagnoses of chronic cystitis and malignancy of the bladder were made.

She entered the Mt. Sinai Hospital on August 30, 1931, on the service of Dr. Edwin Beer and was discharged on November 27, 1931, with the following diagnoses: left renal tuberculosis, arteriosclerosis with psychosis and cerebral changes and lues (?). A summary of her stay is as follows: Complains of frequency, dysuria, and hematuria for 6 months. X-ray films of the genito-urinary tract on August 31, 1931, revealed normal right kidney; left kidney not visualized; numerous calcific shadows over both kidneys.

Roentgenograms of the chest on August 31, 1931, revealed nothing except some cardiac hypertrophy. Cystogram on September 2, 1931, was normal. Electrocardiogram on September 1, 1931, showed left ventricular preponderance. Cystoscopy on September 1, 1931, by Dr. Beer, revealed bladder urine to be turbid; right indigocarmine excretion was strong. Left ureter orifice was retracted, mesial lip converted into an extensive polypoid mass, the orifice being congested and patulous. Right ureter easily catheterized. Left ureter obstructed at 21

Specimens	Bladder	Right	Left
Indigocarmine		Strong	Poor
Microscopic		Negative	Loaded with white blood cells
Sediment for tuberculosis	Negative	Negative	Negative

Fig. 3. Cystogram of Case 1 (B. L.) taken April 13, 1929, showing the normal bladder capacity and the restoration of normal contour 1 year after the patient had received antiluetic treatment.

centimeters, 20 cubic centimeters of purulent urine aspirated.

Tissue punched from the polypoid mass reported as acute inflammation; no evidence of tuberculosis. Guinea pig inoculations of both the right and left specimens were negative for tuberculosis.

However, Dr. Beer felt he had enough evidence to warrant an open operation, and on September 4, 1931, a left nephrectomy was performed. The specimen was reported to show tuberculosis of the left kidney with atrophy and tuberculosis of the ureter.

Later, the bladder urine taken on September 3, 1931, gave a positive result for tuberculosis, on animal inoculation. Cultures from both kidneys were negative. On September 1, 1931, Wassermann was negative and spinal tap was not made. Following the operation, an extensive wound infection developed which required dakinization and healed with great difficulty. Specimens punched from the wound failed to reveal any tuberculosis, either histologically or on guinea pig inoculation.

Frequency and dysuria persisted and on September 28, 1931, a second cystoscopy showed right ureter normal. The left ureter was not definitely seen, but the papillomatous mass had entirely disappeared. Now an irregular ulcer was seen on the posterior wall and one behind left ureter. Several examinations of the bladder urine after operation were negative for tubercle bacilli. Urine became clear and at last the wound began to heal, but the patient developed a psychosis which was considered to be on an arteriosclerotic basis. The consultants were not definitely aware of the luetic history.

The patient was admitted to the X Hospital on December 8, 1931, and died on December 13, 1931. The diagnosis was general arteriosclerosis; hemorrhage into cerebrum; and postoperative wound following left nephrectomy. The laboratory findings just prior to death were: urine, 1010; albumin, positive; sugar, none; some white blood cells. Blood examination showed hemoglobin, 70 per cent; red blood cells, 3,800,000; white blood cells, 14,000; polymorphonuclears, 76 per cent; lymphocytes, 24 per cent; Van den Bergh, negative; sugar, 105. Blood Wassermann was negative. Spinal fluid was clear; smear showed no tubercle bacilli; culture, sterile; albumin, 2 milligrams; globulin, negative; sugar, 100 milligrams.

An autopsy was not obtained.

A case presenting the classical signs of bladder syphilis is described. The patient gave a history of venereal infection; there was evidence of activity as demonstrated by the skin lesions; the blood Wassermann was positive and lesions which could not be accounted for on any other etiological basis were seen to disappear promptly on the administration of antiluetic treatment. The patient remained well for a period of about 2 years; the urine continued to be clear and cystoscopy more than a year after the initial examination revealed a normal bladder. This set of facts certainly places this case in the category of the many others, most of which were not so thoroughly studied. However, subsequent follow-up revealed that the patient actually suffered from renal tuberculosis which was probably complicated by tuberculosis of the bladder. It seems reasonable, therefore, to assume that the patient originally suffered from renal tuberculosis complicated by bladder manifestations. When these were first brought to the attention of the writer, the patient suffered a concomitant active syphilitic infection. Although one would be led to believe that the bladder manifestations were originally syphilitic in the absence of confirmatory bacteriological examinations and animal inoculation, the probability still rests with their being tuberculous. There only remains to explain the rapid response to treatment. It seems that almost any condition would improve in the presence of syphilis when the latter is treated. Furthermore, it is probable that the left urinary tract was temporarily closed off, so that the urinary signs and symptoms would naturally subside. This state of affairs is well known to occur in genito-urinary tuberculosis and calycine involvement. The operative specimen in this case showed a shut off calyx in the upper pole and active lesions below it.

CASE 2. This case was originally reported by Dr. Leo Edelman in the *Journal of Urology*, 1928, 20: August.

Fig. 4. Cystoscopic appearance of the villous papillomatous growth observed by Ajamil (Case 155 in chart).

S. H., male, aged 49 years, private patient of Dr. Beer, was seen by him April 27, 1922, on account of frequency and cloudy urine which had existed for about 10 weeks. He had gonorrhea and syphilis in 1901 at which time he received antiluetic treatment and has had no symptoms since then, the Wassermann reaction always being negative. In addition, he had innumerable prophylactic urethral injections of sulphocarbolate of zinc.

Prior to consulting Dr. Beer, the patient was subjected to cystoscopic examination by another urologist who diagnosed his condition as carcinoma engrafted upon an old syphilis and treated him with radium packs and bladder irrigations. Cystoscopy by Dr. Beer, April 27, 1922, showed the anterior and lateral walls of the bladder to be normal, but the floor and trigone were covered with polypoid edema most marked in and about the ureteral orifices and extending well down to the sphincter. The whole picture suggested a very intense localized cystitis perhaps due to some extravesical inflammatory focus. Several specimens were excised for microscopic study. Rectal examination showed the presence of marked induration about the prostate, possibly due to the effect of the radium packs. The physical examination showed no abnormality. X-ray examination of the genito-urinary tract and a cystogram made on May 2, 1922, showed no abnormality. The late Dr. F. S Mandlebaum examined the specimens and reported the following:

"Microscopic examination of the specimens removed from S. H. shows edematous and congested bladder wall and numerous small, rounded inclusion epithelial cells of somewhat cystic character. In addition there are several areas of glandular acini the cells of which are large and mucinous in nature. These glandular elements do not belong to normal bladder structures. Is it possible that tissue from rectal wall must be considered in identifying the latter? The specimen does not show any evidence of tumor formation in the tissue seen."

It was thought from the cystoscopic examination and previous history that the condition was a localized luetic disease, and in spite of the negative Wassermann, the patient was given mercury and potassium iodide with marked improvement. On June 8, 1922, the patient had gained 12 pounds, the urine was clear, and the frequency had disappeared. On that date, the patient was again examined by cystoscope and there was still present bullous edema extending from the neck up over the trigone and posterior wall of the bladder. The mucosa in this region was deep red in color containing here and there a very evident, white, spherical, minute body. To corroborate the microscopic report, several pieces were excised. The microscopic report by the late Dr. F. S. Mandlebaum on these specimens is as follows:

"Microscopic examination of the specimen marked No. 1 removed from S. H.'s bladder shows a chronic inflammatory process with edema of the submucosa and marked cystic dilatation of the glands. Specimen No. 2 shows practically the same lesion in addition to some degenerative process in the stroma not unlike any early amyloid change. The nodules are almost completely covered with bladder epithelium and represent, in all probability, a polypoid process of the mucosa due to the action of some chronic irritant. All evidence of tumor formation, in the true sense, is absent in all the material examined."

After this date the patient remained perfectly well taking some more mercury and iodides until March 5, 1923, when he presented himself having had a recurrence of symptoms. His urine had been cloudy and purulent, his frequency had become very marked, and his bladder capacity much diminished. There was throbbing after urination, and although patient looked very well he had lost some weight. His voided urine on this date was bloody and purulent, his capacity was 1 ounce, and it was impossible to cystoscope the patient properly on account of active bleeding. There was still marked polypoid edema around the sphincter, but no definite tumor was seen. By rectum, the right vesicle was markedly indurated and the prostate enlarged. The urinary examination showed no tubercle bacilli. The patient was again put on antisyphilitic treatment with neosalvarsan, his symptoms rapidly disappeared, the urine became clear and he gained about ten or fifteen pounds. In the interval between March 5 and March 27, 1923, the patient reported that he had consulted another urologist, who had cystoscoped him and advised operation.

On March 27, 1923, the capacity had increased to 6 ounces and the neck of the bladder seemed almost normal in appearance. The posterior part of the trigone and the post-trigonal area were occupied by a polypoid mass which obscured both orifices. As on the first cystoscopy the year before, the lateral and anterior walls were normal. The picture suggested an extravesical inflammatory focus with secondary involvement of the bladder wall. It was thought that the condition had primarily begun in a suppurating seminal vesicle with possible perforation of the bladder.

On April 4, 1923, the patient again had a cystoscopic examination and several specimens were removed. At this examination the polypoid edema was much less marked, but it seemed to be most developed over the position of the right seminal vesicle. The urine was clear, and rectal examination showed a marked induration above the prostate. The patient at this time was practically normal and had no complaints. The microscopic report of the specimens removed at this cystoscopy is as follows:

"Microscopic examination of tissue removed from S. H's bladder shows marked edema of the subepithelial structures and slight cystic dilatation of the glands. There is no evidence in the specimen of the presence of a tumor. Comparison with previous specimens shows considerably less glandular dilatation and absence of the peculiar mucinous glands."

STATISTICAL SUMMARY OF 158 CASES OF SYPHILIS OF THE BLADDER

Age varies from 6 to 71.

	Cases
Sex:	
Males	75
Females	64
Not mentioned	19
History:	
Positive history of lues or treated for lues	61
No history of lues	89
Active lesions present	28
History of gonorrhea	21
Blood Wassermann:	
Positive (+)	83
Negative (−)	22
Not done	53
Cystoscopic findings: (Usually a combination of the following lesions was present):	
Ulcers	71
Papules	31
Papillomata	21
Tumors	17
Macules and erosions	13
Cystitis (only)	10
Leucoplacia	5
Fistula	4
Type of treatment:	
None	14
Antiluetic (not specified)	67
Arsenicals (usually salvarsan, neosalvarsan or one of these with mercury, bismuth or iodides)	41
Mercury (alone or only with iodides)	22
Iodides alone	6
Bismuth (alone or with iodides)	8
Cystoscopic control following antiluetic treatment:	
Controlled	101*
Not controlled	56
Cured	76
Improved	56
Unimproved	8
Died	7

Recurrences specifically mentioned:
5 cases; Nos. 58, 92, 93, 86, 104.

Associated with tuberculosis:
Cases 74, 134. Tuberculosis was excluded in only 27 cases by negative smears, cultures or animal inoculation.

Histopathology:
Reported eight times. Only one reported typical syphilitic histopathology. Two are claimed to have shown specific pathology, but are not reported in detail. The other five cases reporting histology in detail give a description of non-specific inflammation.

*Time varied from one day to a few years.

On February 12, 1926, the last cystoscopy performed by Dr. Beer showed only some polypoid edema about the sphincter. The prostate was moderately enlarged per rectum, patient was voiding three or four times during the day and occasionally once at night and his general condition was good. On September 14, 1934, the patient's physician reported that he was in perfect health.

The second case is that of a male patient who probably had syphilis about 20 years prior to his first observation when he developed symptoms of cystitis and presented a cystoscopic picture suggestive of neoplasm. It was thought that he probably had involvement of the bladder wall secondary to some extravesical disease in the seminal vesicle. Specimens excised from the inflamed localized polypoid bladder wall revealed muciparous glands suggesting rectal mucous membrane. He responded rapidly to mercury and iodides, but developed a recurrence a year later. This time neosalvarsan added to the antiluetic treatment produced a rapid disappearance of the symptoms.

SUMMARY

1. A review of the literature since 1900 with an intimate analysis of 158 cases is offered.

2. There is a marked laxity in the reporting of cases which are neither thoroughly studied nor followed and adequately controlled.

3. Only eight investigators have subjected the lesions to microscopic study. Only one shows typical histopathology. Two are claimed to have shown specific histopathology, but are not reported in detail. The 5 others give descriptions of non-specific inflammation.

4. The diagnostic criteria used in most of the cases are described.

5. Two cases, one of which possesses all these diagnostic criteria, are described in detail, demonstrating the pitfalls which are encountered in the presence of bladder disease and concomitant syphilis.

6. Not one of the cases described measures up to the standard set by Young, who maintains that the spirochæta must be demonstrated in the lesions.

BIBLIOGRAPHY

1. Aschoff, Ludwig. Pathologische Anatomie. Jena: G. Fischer, 1913.
2. Chocholka, E. F. J. d'urol., 1931, 31: 575–587.
3. Ibid. 1923, 16: 85–98.
4. Ibid. 1928, 25: 513–520.
5. Ibid. Ztschr. f. urol. Chir., 1926, 21: 134–181.
6. Correa, B. Folha med., 1929, 10: 442–444.
7. Danforth and Corbus. Surg., Gynec. & Obst., 1921, 31: 219–226.
8. DeGouvea, J. A. J. d'urol., 1924, 18: 388–395.
9. Denslow, F. M. J. Am. M. Ass., 1918, 70: 154.
10. Duvergey. Cong. d'urol., 1925. Cited by Chocholka (5).
11. Friedman. Paris méd., 1926. Cited by Chocholka, (4).
12. Graff, K. Beitrag zur Kenntniss du Blasensyphilis Dissertation, Freiburg, 1906.
13. Kaufman, E. Pathology. Philadelphia: P. Blakiston's Son & Co., 1929.
14. Levy and Tripoli. Am. J. Obst. & Gynec., 1933, 25: 743–746.
15. Levy and Zimmerman. J. Urol., 1919, 3: 407–410.
16. MacCollum, W. G. Textbook of Pathology, 1916.
17. McCarthy, L. Histopathology of Skin Diseases. St. Louis: The C. V. Mosby Co., 1931.

TABULATION OF CASES

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
1	Matzenauer	1900 F 22	Lues, 4 years			Papilloma-like projections resembling villosities. Ulcer on superior wall of urethra	None	
2	MacGowan	1901 M	Lues, 10 years			Papilloma-like projections behind right ureter. Concentric ulcers with hard infiltrated edges	None	
3	LeFur	1902 M	Lues, 8 years. Treated irregularly. Developed luetic patches in the pharynx while under observation		Hematuria, 2 years	3 ulcers on trigone	After antiluetic treatment—complete recovery in short time. Control—white scars. Irregular hard nodule in prostate became normal after antiluetic treatment	No gonococci. No bacteria in urine
4	Graff	1906 M 56	Painless doughy swelling of both testicles			Tumor-like growth with central defect and papillary proliferation at edges. Suprapubic operation—ulcer cauterized	6 weeks after operation and antiluetic treatment discharged cured	Excised tissue—chiefly necrotic cell masses and bladder epithelium which did not show tumor formation
5	Asch 1st case	1911 F 28	Ulcer on labium 15 mos. ago. Inguinal glands hard, enlarged and painless			Scattered superficial round defects with whitish bases like luetic patches	2 wks. after mercury inunctions symptoms began to improve. 4 wks. later symptoms almost gone; bladder showed slight redness; 6 wks. later bladder normal. 1 yr. later control also normal	No tubercle bacilli in urine by microscopic or inoculation
6	2d case	1911 M 45	Lues, 20 yrs. before. Hardly any treatment			Papillæ and ulcer surrounded by papillæ		No gonococci or tubercle bacilli
7	3d case	1911 M 35	Chancre 20 yrs. ago. Treated superficially. Ulcer on right thigh 5 mos.			Large gummatous ulcer in fundus	4 days after arsphenamine. Ulcer on thigh and bladder symptoms disappeared and control showed normal bladder	
8	Pereschiwkin 1st case	1911	Luetic lesions on skin and mucous membranes			Several ulcers near left ureter	Mercury inunctions produced rapid amelioration of symptoms	
9	2d case	1911	Luetic lesions on skin and mucous membranes			Several small ulcers in summit	Mercury inunctions produced rapid amelioration of symptoms	
10	3d case	1911	Luetic lesions on skin and mucous membranes			Small ulcerations scattered all over bladder, sphincter edematous	Mercury inunctions produced rapid amelioration of symptoms	
11	Posados	1911	Lues, 19 yrs. Cutaneous gummata		Hematuria, 14 mos.	Gummatous ulcer	After antiluetic treatment, lesion ½ size. Later control—complete cure	No tubercle bacilli
12	Habenern	1911		Positive		Large gummatous ulcer on trigone and tumor on lateral wall	20 days after 1 arsphenamine ulcer disappeared and tumor was "reduced to small size"	
13	von Engelman 1st case	1911 F 60	No luetic history. (See Column 7)		Hematuria, 6 mos.; no frequency or dysuria	Tumor 3 cm. near 1. Ureter with ulcerated surface diagnosed as carcinoma	Later determined patient had lues 20 yrs. ago. Ulcers healed rapidly under mercury and tumor disappeared in a few wks.	
14	2d case	1911 M 46	Lues 15 yrs. ago. Mercury and potassium iodide. Paralysis left leg 1 yr. Disappeared after mercury		Hematuria, 3 mos.	Round tumor, hazel-nut size near right ureter with ulcerated surface and papillary changes	After 30 mercury inunctions lesions disappeared and a red spot was found in their place	

TABULATION OF CASES—Continued

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
15	3d case	1911 F 47	Paralysis both legs 1 yr. 3 abortions in 20 yrs. Luetic myelitis		Frequency and dysuria, 1 mo.	Large ulcer near left ureter. Other ulcers summit and lateral wall 5 cms. with papillæ	After antiluetic treatment—slow but progressive improvement. After 2 mos. with irrigation—control-normal bladder with white scars	Gram positive diplococci, streptococci, no tubercle bacilli
16	Margoulies	1912 F 41	White scars on legs. 1 miscarriage			3 excrescences—bean size behind left ureter. Diagnosis—carcinoma	Potassium iodide produced rapid improvement 1 mo. later control—tumors disappeared leaving insignificant scars	
17	Michailof	1912 F 39		Positive	Hematuria, 5 yrs.	Rows of vesicles on lateral and superior wall, each surrounded by red zone	Hemorrhage came from left kidney. Bladder symptoms disappeared promptly under antiluetic treatment. Control—lesions healed	
18	Mucharinsky	1912 M	1 yr. ago—chancre, roseola and treatment			Hyperemia of sphincter, midlobe intruded, coin-size ulcer on fundus	Complete healing after antiluetic treatment. Catheter used for 2 weeks	
19	Picot	1912 M 53	Lues denied. Operation—vesical calculi 1 yr. later—vesico-rectal fistula	Positive	Hematuria, 1 yr. frequency, dysuria, 8 yrs.	Left ureter large, gaping. Large projections like parquetted floor. Plaques with halos and small ulcerations. Fistulous orifice ¼ cm.	No treatment. No control.	
20	Doureoux	1913	No subjective symptoms			Red patches similar to luetic exanthema. Lesions seen during routine cystoscopy	Control after antiluetic treatment verified cure	
21	Picker	1913		Negative	Frequency, dysuria	¼ cm. yellow prominence near right ureter	Complete healing after antiluetic treatment	
22	Gayet and Favre 1st case	1914 M 66	Tabetic	Positive	Hematuria, frequency, dysuria, 15 mos.	Median lobe enlarged with ulcer over median lobe. 2 other ulcers near left ureter covered with papules	After 6 mos. weekly calomel and potassium iodide ulcers healed. Hematuria disappeared at beginning of treatment	
23	2d case	1914 F 55	Lues denied. 7 yrs. ago had sudden perforation at juncture of hard and soft palate		Hematuria, frequency, dysuria, sudden	Numerous papillomata with cerebral convolutions	Arsphenamine begun before bladder visualized. 5 days later papillomata seen. Later only ridges seen	
24	3d case	1914 F 35	11 yrs. ago chancre of lip		Hematuria, frequency, dysuria, 15 days	Trigone red with median projection (like prostate), Sphincter red	Simple rubbing brought about complete cure	
25	Shapira	1915 M 46	Chancre 17 yrs. ago and discharged as cured. 15 yrs. later rash diagnosed as luetic. Wassermann became negative 2 yrs. ago after 5 arsphenamine when rash disappeared. After 1 injection arsphenamine Wassermann became positive	Positive	Frequency, dysuria, 5 mos.	Slight congestion, very trabeculated. Ulcerated patch 2 cms. near left ureter and another smaller one nearby	After mercury and potassium iodide and local treatment, bladder symptoms disappeared and control showed normal bladder and negative Wassermann	
26	Pedersen 1st case	1916 M 71	Lues 50 yrs. with only oral medication. Finally cured 10 yrs. ago with intensive treatment		Hematuria, frequency, dysuria, 5 yrs.	Retention. Cystoscopy—difficult. Diagnosis: neoplasm (?)	Antiluetic treatment only partial success. After 1 mo. fleshy mass with villous formation and necrosis. 9 mos. after antiluetic treatment bladder improved	

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
27	2d case	1916 F 44	25 yrs. ago had child with congenital lues treated successfully		Hematuria, frequency, dysuria, 7 yrs.	After 5 mos. with intramuscular injection condition improved and cystoscopy showed ulcer	Under intramuscular injection bladder symptoms subsided in 10 days. No control	
28	3d case	1916 M 34	No luetic history. Gumma in supraspinous fossa	Negative		Flat infiltration supposed to be due to insertion of bougie for stricture. Marked cystitis	After 4 wks. intramuscular injection control—improved and wound in supraspinous fossa healed. Patient disappeared and returned 9 mos. later when control—further improved with infiltration ½ size	
29	4th case	1916 M 62	No luetic history. Residual—1 dram		Frequency	No cystoscopy	After antiluetic treatment symptoms disappeared. No control	
30	5th case	1916 F 30	Never free from bladder symptoms because of 2 gonococcic infections from husband. Right nephrectomy 2 yrs. ago for infection of right kidney with stricture of right ureter and ulcer at right ureter	Positive		Cystoscopy negative 8 mos. later ulcer with punctate spots in bladder	Antiluetic treatment followed by improvement. No control	
31	Nilson	1916 M 44	Lues denied. Gonorrhea 4 years ago. Ulceration of nose did not heal readily. 1 epididymis hard		Hematuria, 5 yrs.	Numerous ulcerations and cicatricial changes	Died 3 yrs. later of aneurism of aorta although normal conditions in bladder were restored. Patient failed to complete treatment	3 tests for tubercle bacillus negative
32	Gouvea 1st case	1916 F 55	No history of lues	Negative	Hematuria, frequency, dysuria	Large globular, highly vascular tumor near left ureter. No ulceration	Gradual improvement in symptoms 3 mos. after antiluetic treatment control showed normal bladder	
33	2d case	1916 M 34	Gonorrhea 4 mos. ago and small ulcer on lip which healed under arsphenamine. Pain in kidney		Hematuria, few days	Scattered papules around left ureter which was congested	All bladder symptoms and hematuria yielded to antiluetic treatment	
34	Baker 1st case	1917 F 19	No history of lues. Sex indiscretion admitted		Frequency, dysuria	Mucous membrane on left anterior wall of bladder deep red and livid	Few days after local treatment soft, red spot found on labium majora. Bladder symptoms disappeared after 3 mos. antiluetic treatment	
35	Baker 2d case	1917 F 22	No history of lues. Sex indiscretion admitted. Luetic eruption on labia	Positive	Frequency, dysuria, 5 yrs.	Deep hyperemia of mucous membranes	Marked improvement under antiluetic treatment	
36	Fowler	1917 M 19	No history of lues. Enlarged epitrochlear and inguinal glands	Positive	Hematuria, frequency, dysuria, 3 mos.	Marked cystitis—small ulcer near right ureter suggesting tuberculosis	1 day after arsphenamine marked improvement. 3 mos. arsphenamine and mercury—patient was symptom-free	
37	K. Ries	1917 M 45	Pupils unequal	Negative	Hematuria, 15 yrs.	Gummatous ulcer with red halo	Under arsphenamine and mercury hematuria ceased	
38	Krotoszyner	1917 M 60	Positive luetic history	Positive	Hematuria painless	Small papillomatous tumor near trigone	Lesions disappeared after antiluetic treatment	
39	Watterson	1917 F	Clinical evidence of lues	Positive	Hematuria	Ulcer with small erosions near trigone	Lesions disappeared after antiluetic treatment	

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
40	Wallace 8 cases Corbus 1st case	1918 M 28	No luetic history. Pain in kidney and bladder 3 yrs. ago		Hematuria, frequency, dysuria, 6 mos.	Prostate enlarged. Villous growths on right near sphincter—others near right ureter	Antiluetic treatment followed by complete cure and disappearance of growth	
41	2d case	1918 F 43	No luetic history. 1 miscarriage; 1 stillbirth	Positive	Hematuria, frequency, dysuria	Papules and ulcer on internal sphincter. 3 irregular ulcers on trigone, resembled tuberculosis	Lesions cleared up under antiluetic treatment	
42	3d case	1918 M	No luetic history. Father had lues 30 yrs. ago. Congenital lues presumed	Positive	Hematuria, frequency, dysuria	Ulcerated and nodular trigonitis. Ulcer and few nodes on internal sphincter	Lesions cleared up under antiluetic treatment	
43	4th case	1918 F 30	No luetic history. Operation on kidney. Bladder symptoms 11 yrs.	Positive	Frequency, dysuria, 11 yrs.	2 ulcers near right ureter, several near left ureter, 4 on trigone. Papules and ulcers about internal sphincter	Fatient became apparently well under antiluetic treatment	
44	5th case	1918 F 28	No luetic history. Referred for cystitis	Positive		Papules and ulcers on trigone and near right ureter and sphincter	Fulguration and bladder irrigation unsuccessful. Healed under antiluetic treatment	
45	6th case	1918 M 40	No luetic history. Suprapubic cystotomy 3 yrs. ago for growth	Positive	Frequency, dysuria, 3 mos.	Ulcer of base and trigone. Very inflamed bladder	2 injections of arsphenamine and other antiluetic remedies produced great improvement	
46	7th case	1918 M 29	Gonorrhea 12 yrs. ago. Operation 2 yrs. ago for stone. None found. Papilloma removed	Positive		Ulcerations and villous growth of neck extending to trigone	Under intensive antiluetic treatment growth disappeared and bladder cleared	
47	8th case	1918 M 29	Gonorrhea 14 yrs. ago and recently. Large prostate and stricture of urethra	Positive	Frequency, dysuria	Thickened bladder with distinct gumma near left ureter	Results of treatment not recorded	
48	Denslow	1918 M 23	Chancroid 2 yrs. ago. Gonorrhea 1 yr. ago, continued to date of examination	Positive	Frequency, dysuria, 1 yr.	Papillomatous masses in posterior urethra and around sphincter. Operation-condyloma-like nodules studded base of bladder. Nodules curetted	Under mixed treatment, normal conditions in 3 mos.	Curettings reported: "syphilitic condyloma"
49	Cole	1918 F 34	Treated for lues 12 yrs. ago. Gonorrhea twice 8 and 10 yrs. ago	Positive	Hematuria, 2 yrs. Frequency, dysuria, 6 yrs.	Severe trigonitis with edema. Large crescentic ulcer near right and left ureters	Improved under arsphenamine and mercury 3 mos. later control—white scars. 3 yrs. later no symptoms	
50	Hesse	1918 F 24	Lues denied. Tuberculosis in family	Positive	Frequency, dysuria	Reddish-brown circular papules in fundus	Recovered under antiluetic treatment. No control	No tuberculosis
51	Ringleb	1919 F			Frequency, dysuria	Ulcer with crateriform edge infiltrating rectum and genitalia	Under iodides condition improved. No control	
52	Dansforth and Corbus	1920 F 25	Gonorrhea 3 yrs. ago. Criminal abortion followed by fever. Vesicovaginal septum infiltrated	Positive	Frequency, dysuria, 2 mos.	Infiltrated growth with many peaked projections of papillomatous character suggesting malignancy. Operation—cystotomy-lesion on base not malignant	2 wks. after antiluetic treatment control—improved. 2 mos. later wound healed, general condition good. No further control	Gonorrhea and tuberculosis negative
53	Thompson	1920 M 25	Ulcer of penis 3 mos. ago. Typical roseola and adenitis 4 days. No treatment	Positive	Hematuria, frequency, dysuria, 2 days	Trigone congested. Ulcerating papules near each ureter	Hematuria ceased 1 day after 1 arsphenamine and mercury. 4 wks. after 4 arsphenamine and mercury—no symptoms and control—normal bladder.	No spirochætæ found in urine on dark field

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
54	Boeckel	1920 F	No history of lues. Symptoms of cystitis	Positive		Erythematous plaques	Antiluetic treatment produced rapid cure	
55	Kolischer and Eisenstadt	1919 M 40	History of lues, treated irregularly 10 yrs. ago		Frequency, dysuria	2 grayish spots size of lentil with red halo	No treatment—no control	
56	Chocholka	1921 F 36	Luetic exanthema	Positive	Frequency, dysuria, few wks.	Yellowish papules with red halos near ureters	1 day after neoarsphenamine halos began to disappear. 1 mo. after mercury rubs papules disappeared	Guinea pig test negative. Pirquet negative. Various bacteria in urine
57	Cosacesco 1st case	1921 M 26	Gonorrhea 10 and 8 yrs. ago. No luetic history	Positive	Hematuria, frequency, dysuria, 8 yrs.	20 days after institution of antiluetic treatment observed congestion of mucous membrane	After 5th injection of mercury symptoms were relieved and 1 mo. later symptom-free. 7 mos. later completely cured	Rare diplococcus and gram positive bacteria in sediment. No gonococcus or tubercle bacilli. X-ray negative
58	2d case	1922 F 33	1 abortion. No gonorrhea or tuberculosis	Negative	Hematuria, frequency, dysuria, 14 yrs.	Ulceration	After 2 wks. neoarsphenamine and mercury oxycyanide marked improvement and control showed lesions almost healed. 1 mo. after antiluetic treatment—cured and third cystoscopy showed only scar. Stopped antiluetic treatment and returned 2 mos. later—4th cystoscopy showed ulceration. Mercury oxycyanide and neoarsphenamine started and 10 days later 5th cystoscopy almost healed lesions. 1 mo. after antiluetic treatment—symptom-free and 6th cystoscopy—white scar	No gonococcus or tubercle bacilli
59	R. Picker	1922 M 35	Gonorrhea 18 yrs. ago and 8 yrs. ago. Left orchidectomy and right epididymitis. Treated for lues until 1 yr. ago with mercury 3 mos. ago rash and arsphenamine substituted		Frequency, dysuria	Small yellowish projections with red halo. Papules on left lateral wall. 2 days later yellowish spots fading. After potassium iodide ulcers developed at site of papules	4 days later all lesions showed beginning healing. 1 mo. after 1st cystoscopy lesions almost healed	
60	Farago 1st case	1922 F 26	1 abortion. Husband treated for lues	Positive	Frequency, dysuria, 1 yr.	Small grayish papules and nodules with red halo	After neoarsphenamine several controls showed normal bladder and no symptoms	
61	2d case	1922 F	2 abortions and 1 premature. Skin rash 14 years	Positive	Frequency, dysuria, 1 yr.	Many grayish white papules with red halo on trigone and leucoplacic patch	3 wks. after neoarsphenamine and mercury marked improvement in symptoms and control—most of papules disappeared. 5 mos. later after 2 complete courses—no symptoms and control—normal except for leucoplacia	
*62	Ghiso and Puente	1922 F 57	6 abortions	Negative	Hematuria, frequency, dysuria	Ulceration	16 days after arsphenamine symptoms gradually improved and bladder almost normal	
*63	Pasteau	1922		Positive	Frequency, dysuria	Cystitis and small "tumarchen"	Healed under antiluetic treatment	
*64	Stotoerts	1922		Positive	Hematuria, frequency, dysuria	Ulcer	Healed under antiluetic treatment	

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
*65	Perucci	1922		Positive	Hematuria, frequency, dysuria	Granulomatous ulcer	Healed under antiluetic treatment	
*66	Beuc	1923		Positive	Hematuria, frequency, dysuria	Ulcer	Healed after 4 neoarsphenamine	
*67	Uras	1924		Positive	Frequency, dysuria	Ulcer	Healed under antiluetic treatment	
*68	Cirillo	1924		±	Frequency, dysuria	Appearance of tertiary lues	Healed under antiluetic treatment	
*69	Aranda	1924				Roseola	Healed under antiluetic treatment	
*70	Girard 1st case	1925	Cumma cubiti	Positive	Frequency, dysuria	Ulcers and cystitis	Healed under antiluetic treatment	
*71	2d case	1925		±	Dysuria	Macules and mulberry appearance		
*72	3d case	1925		±	Dysuria	Macules and mulberry appearance		
73	Coll	1925	Lues			Appearance of cystitis and gumma	Healed under antiluetic treatment	
74	A. Peterson 1st case	1924 M 45	Gonorrhea 19 yrs. ago. No luetic history	Positive	Frequency, dysuria, 8 mos.	Diffuse cystitis with edematous area Suprapubic cystostomy revealed ulcer	Neoarsphenamine and mercury for 5 wks. and discharged from hospital without improvement. Died 3½ mos. after operation. Diagnosis—pulmonary tuberculosis	No tubercle bacilli in urine
75	2d case	1924 F 39	Pain over right kidney, red blood cells in urine and X-ray film showed suspicious shadow over right kidney	Positive		2 ulcers near right ureter which could not be catheterized	Acites. Diagnosis of lues of bladder right kidney and liver. Severe reaction after arsphenamine. After 25 mercury felt well. No acites, no control	No tubercle bacilli in urine
76	Luttichau	1925 F 39	Treated for cystitis for a long time	Positive		Inflamed bladder	After antiluetic treatment symptoms and signs disappeared	
77	DeGouvea 1st case	1924 F 60		Negative	Frequency, dysuria	Lobulated tumor	15 days after antiluetic treatment marked improvement. 5 wks. after mercury and iodine no symptoms and control—scar and normal b adder	
78	2d case	1924 M 34	Left renal colic and hematuria. X-ray showed no calculus but left kidney larger		Hematuria	Small red spot with superficial ulceration	Antiluetic treatment cured him	No tubercle bacilli
79	3d case	1924 M 32	No venereal history	Negative	Hematuria, frequency, dysuria	Irregular tumor surrounded by red zone	Treated with mercury and iodides and later learned that he was cured	
80	4th case	1924 M 32	Gonorrhea and chancre 5 years ago		Frequency, dysuria	Irregular whitish gray spots	All symptoms disappeared after antiluetic treatment and control showed normal bladder	
81	5th case	1924 F 55			Frequency, dysuria, 1½ yrs.	Sessile tumor. Suprapubic cystotomy 12 days later revealed tumor over trigone	40 days after neoarsphenamine and iodides—cured and control showed normal bladder	Chronic inflammation—no sign of malignancy. No mycosis

*Cases 62 to 72 inclusive are cited by Chocholka in 1926.

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
82	6th case	1924 M 49	Left renal colic. Gonorrhea and soft chancre 20 years ago	Negative	Hematuria, frequency, dysuria	Large irregular tumor bleeding easily	20 days after antiluetic treatment tumor smaller. 4 wks. later—large scar at site. No symptoms	
83	7th case	1924 M 53	Tabetic, no residual, prostate—negative		Hematuria, frequency, dysuria	Infiltrated areas with hyperemia and bullous edema	Antiluetic treatment with 914. Almost complete disappearance of symptoms. 2 mos. later control—normal bladder	
84	8th case	1924 F 36	Operation for salpingitis 10 years ago. Right renal colic. X-ray negative	Negative		Bullous edema with ulcerations and papillomatous changes	2 mos. after antiluetic treatment control—normal bladder	
85	9th case	1924 M 30	No luetic history. Right renal colic. X-ray small shadow near right ureter in pelvis		Hematuria, frequency, dysuria	Ulceration near right ureter. Check-up X-ray showed shadow to be outside of ureter	Rapid relief after bismuth, mercury and iodides. 3 wks. later control—scar at site of ulcer	
86	Saelhof	1925 M 34	Gonorrhea 15 yrs. ago with relapses 10 and 13 yrs. ago. Argyll Robertson pupils. Papilledema. Aneurism of aorta. Spinal fluid Lange test suspicious of cerebrospinal lues, Wassermann positive	Positive	Hematuria, frequency, dysuria, 2 yrs.	Small irritable bladder, 5 small deep ulcers	2 wks. after mercury rubs and neoarsphenamine symptoms improved. Patient disappeared and returned in 1 yr. with same symptoms and added cerebrospinal symptoms. Mercury and arsphenamine started but patient died 20 days later	Ulceration through mucosa into bladder wall with marked infiltration of plasma and round cells. Proliferation of interstitial tissue and only slight endarteritis. Guinea pig negative, no tubercle bacilli
87	Lucri	1925 F 34	Two abortions	Positive	Frequency, dysuria	8 small lentil size papules	After 6 injections mercury and sulpharsphenamine felt well. After 8th injection control—all papules disappeared and small hemorrhagic points instead. 2nd control 1 mo. later—same	Staphylococcus,colon bacillus. No tubercle bacilli. Guinea pig. Negative. Pirquet—negative
88	Barabas	1925 M 36	Gonorrhea 5 yrs. ago. 4 antiluetic courses previously. No urethral discharge but intracellular diplococci in sediment	Positive	Hematuria, frequency, dysuria, 3 days	5 grayish-white small papules with red halos	Hematuria disappeared after 2 neoarsphenamine. After 4 neoarsphenamine injections control—normal bladder	
89	Blanc and Negro	1925 F 37	Treated many years for lues. Emitted gas from urethra 6 mos.	Negative	Frequency, dysuria, 5 mos.	Vesico-intestinal fistula shown by cystoscopy and cystogram	After 48 injections of biodure and 2 series neoarsphenamine Wassermann negative and 1 yr. later after continued antiluetic treatment control—only slight edema. Cystogram—no fistula. No symptoms	
90	Riley 1st case	1926 M 34	Gonorrhea 18 yrs. ago. Oper.—stricture urethra and perineal abscess 8 yrs. ago	Positive	Hematuria, frequency, dysuria	Stricture in deep urethra dilated gradually. 10 days later red edematous bladder with small capacity and several ulcers	After 4 wks. antiluetic treatment symptoms subsided but urine remained turbid. Control—ulcers healed. 3 mos. later control—normal bladder with scar	
91	2d case	1926 M 58	Chancre 25 yrs. ago	Positive	Frequency, dysuria, 1 yr. Hematuria, 6 mos.	Elongated ulcer near left ureter	Hematuria ceased after 3 neoarsphenamine. No control cystoscopy	
92	Avramovici	1926 F 30	Treated for lues for 4 yrs. until 2 yrs. ago. No history of gonorrhea	Positive	Hematuria, frequency, dysuria, few mos.	Small ecchymotic area and small ulceration near sphincter	Symptoms subsided after 6 neoarsphenamine and 6 mercury oxycyanide. 3 mos. later control—normal bladder. 1 yr. later same symptoms but no control. 1 mo. after 7 neoarsphenamine and 8 mercury oxycyanide symptoms disappeared and urine was clear	No spirochætæ in urinary sediment

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
93	Rothschild	1926 F 67	No gonorrhea. Husband luetic	Negative Later ±	Frequency, dysuria, 6 mos.	Papules with condyloma-like lesions with red halo. 1 mo. after irrigation with silver nitrate, only 2 papules remained. These papules persisted until 4 mos. later when they were coagulated with high frequency	Symptoms returned in a few wks. and control—8 mos. after 1st cystoscopy—same findings. 1 mo. after silver papules disappeared again. Patient not seen for 7 yrs. returning with frequency and dysuria 3 wks. Well in 7 years' interval. Last cystoscopy showed dark red patches	
94	Molina 1st case	1927 F 30	No venereal history	Positive	Hematuria, frequency, dysuria	Ulcers	3 wks. after 6 injections of iodo-bismuth control—normal bladder	
95	2d case	1927 F 26		Positive	Hematuria, frequency, dysuria, 3 mos.	Ulcers resembling tuberculosis	After iodo-bismuth control—scar in normal bladder	
96	3d case	1927 M 73	Old luetic treated only with mercury. Renal colic with passage of small stones. Incomplete retention due to prostate		Hematuria, frequency, dysuria	3 vesical calculi, superficial ulcers and cystitis. Litholopaxy followed by lavage but symptoms continued	After 4 iodo-bismuth improvement in all symptoms. After 15 injections control—normal bladder	
97	Gautier	1927 M 44	Lues 9 yrs. with rectal ulcers. Treated for 5 yrs. No treatment in last 4 yrs. Infiltration above prostate	Positive		Gummatous ulcer with crateriform edge. Several petechial spots	1½ mos. after 12 bismuth and 6 stovarsol—no symptoms, no rectal infiltration and control—normal bladder	
98	Papin	1927 M 44	Chancre 9 yrs. ago. Treated 2 yrs. Wassermann negative. No treatment since. Large left testicle. Right kidney large and tender. X-ray negative	Positive	Hematuria, 1 yr. Frequency, dysuria, 3 mos.	Number of lentil size papules. 30 days after mercury oxycyanide and 2 neo-arsphenamine per week testicle smaller, right kidney smaller, urine clearer, and control—papules fading	10 mos. with mercury and potassium iodide all symptoms subsided and considered cured	
99	Turner 1st case	1927 M 64	Suprapubic cystotomy for bladder ulcer 10 yrs. ago. No luetic history. Large boggy prostate. Retention 4 mos.	Positive	Hematuria, 4 mos. Frequency, dysuria, 10 yrs.	Solitary ulcer found on suprapubic cystotomy. Diagnosis—cancer	Under antiluetic treatment hematuria subsided and ulcer healed. 3 wks. later 2d stage prostatectomy—uneventful recovery. 6 wks. later control—normal bladder. 6 yrs. later slight frequency and dysuria cured by dilatation	
100	2d case	1927 M 42	Symptoms followed appendectomy with drainage and catheterization. Prostate large, boggy, tender. Vesicles nodular	Positive	Hematuria and frequency, 1 yr.	No residual. Red and edematous mucous membrane. Ulcer near left ureter	Symptoms improved under antiluetic treatment but patient died 2 years later—cause unknown	
101	3d case	1927 M 61	Chancre 8 yrs. ago, no treatment. Prostate large, boggy, indurated area. Right seminal vesicle. Retention ½ ounce	Positive	Hematuria, frequency, dysuria, 2 yrs.	Prostatic ring contracted. Mucous membrane red and edematous. Ulcer with papillomatous nodules	No symptoms 2 mos. after antiluetic treatment. No control	
102	4th case	1927 F 29	No luetic history	Positive	Frequency, dysuria, 1 yr.	Ulcer with bullous edema	5 wks. after antiluetic treatment control—ulcer healed. Slight congestion. No symptoms	
103	5th case	1927 F 51	No luetic history. Hysterectomy for tumor 10 yrs. ago. Never pregnant. Mild kraurosis. Band-like constriction in adnexal region rigidly holding base of bladder	Negative later positive		Ulcer with bullæ	2 mos. after antiluetic treatment greatly relieved except small bladder capacity	

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
104	6th case	1927 M 56	No luetic history	Positive	Hematuria, 18 mos.	Papillomatous tumor with bleeding from right ureter	3 wks. after antiluetic treatment hematuria ceased. 3 mos. later much improved, control—normal bladder. Returned 1 yr. later with positive Wassermann and same cystoscopic picture. Now under antiluetic treatment	
105	Pugh 1st case	1927 M 49	Lues 10 yrs. ago treated 2 mos. Hard prostate. Treated with sounds	Positive	Hematuria, frequency, dysuria	Relaxation of sphincter. Superficial ulceration and small growths, also present in prostatic urethra	Marked improvement in 3 mos. under antiluetic treatment. Then patient disappeared	Tissue taken from growths reported as syphilitic
106	2d case	1927 M 49	Large and tender vesicles. Repeated fulguration for bladder mass	Positive	Hematuria, frequency, dysuria, 4 yrs.	Papilloma-like mass near right ureter	Apparent subsidence of all symptoms under antiluetic treatment	Section taken from mass suggested syphilis
107	3d case	1927 F 63	General adenopathy, especially epitrochlear. Board-like hardness of bladder neck per vagina	Positive	Hematuria, frequency, dysuria, 1 yr.	Large area suggesting cystitis cystica found to be nodular on attempting puncture—no fluid obtained	Under arsphenamine and bismuth local condition improved satisfactorily	
108	4th case	1927 M 64	Treated 10 yrs. ago for lues irregularly	Positive	Hematuria, frequency, dysuria, 2 wks.	Engorgement of bladder. Several small bead-like ulcers near both ureters	Under arsphenamine, mercury and bladder irrigation, condition cleared readily	
109	5th case	1927 M 44	Treated for penile lesion 10 yrs. ago and ulcerated septum 2 yrs. ago. Prostate and vesicles tender	Positive	Frequency, dysuria, 6 mos.	Mass on trigone between ureters suggesting cancer	Placed on antiluetic treatment. He was doing well when he disappeared	
110	A.A.Palma 1st case	1927 F 37	Several abortions		Hematuria, frequency, dysuria, 10 mos.	Several elevated nut-sized tumors near right ureter and lesions resembling bilharziasis	After 20 novasural control—normal bladder. Ulcer of cervix healed	No bilharziasis in urine. No tubercle bacilli. Guinea pig negative
111	2nd case	1927 M	Operation for inguinal hernia		Frequency, dysuria	Slight enlargement of prostate producing slight retention. 2 ulcers on trigone	Mercury resulted in cure. No control	
112	3rd case	1927 M	Urethral discharge many years in spite of negative smear		Frequency, dysuria	3 ulcers near right ureter and hemorrhagic spots on trigone	Cured with 10 injections of novasurol. No control	
113	4th case	1927 M 30	Chancre 3 yrs. ago. Gonorrhea 10 yrs. ago. Treated for gleet 3 mos. Smear for gonococci,+			Ulcers on trigone	After 914 and novasurol, urine cleared, no symptoms and control—normal bladder	
114	5th case	1927 22	Tabetic crises (?)		Hematuria, frequency, dysuria, 3 mos.	3 ecchymotic areas	Neoarsphenamine resulted in complete cure. No symptoms. No control	
115	6th case	1927 F 25	Lues denied. Pregnant 3 mos.		Hematuria, frequency, dysuria, 7 yrs.	Deeply congested mucous membrane of entire bladder	Improved after 2 mercury oxycyanide. After neoarsphenamine hematuria, frequency, dysuria disappeared and control hyperemic areas	
116	Nitkin 1st case	1928 F 29	No luetic history	Negative	Hematuria, frequency, dysuria, 1 yr.	3 hazel-nut elevations on trigone. Operation incrustations removed and ulcers discovered. Thermocautery and silver nitrate—no effect	Potassium iodide produced prompt relief. 1½ mos. later control—normal bladder and hyperemia at ulcer sites	

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
117	2d case	1928 F 47	No luetic history	Positive	Frequency, dysuria, Sev. yrs.	Several yellowish elevations on trigone	3 wks. after antiluetic treatment symptoms disappeared and control—normal bladder	
118	K. Ries 1st case	1928 M 6	Periodic hematuria 1½ yrs. Father luetic. Elder brother blind	Positive	Hematuria, frequency, dysuria, 1½ yrs.	None	Hematuria subsided after mercury inunctions in several wks. No symptoms after several mos.	
119	2d case	1928 M 45	Headaches, cachexia and anemia. Unequal pupils and red optic discs	Positive	Hematuria, 15 yrs.	Gummatous ulcer near left ureter. Tumor extends over trigone 3 cms.	Under mercury inunction and arsphenamine, hematuria disappeared in several wks. Control—normal bladder	No tubercle bacilli. No gonococci
120	Chocholka 1st case	1928 F 42	Many abortions. Peration-fibroid uterus 1 yr. ago			Papillomata on posterior wall. Electrocoagulation painful and without effect	2 mos. after antiluetic treatment symptoms disappeared control—scar	
121	2d case	1928 M 45	Diabetes and nervosite. No luetic history		Hematuria, frequency, dysuria	Trabeculated hypertrophy with incrustation surrounded by inflamed mucous membrane and pseudo-membrane	Succumbed to peritoneal crisis before operation was possible. Diagnosis—parasyphilis	
122	3d case	1928 F 39	Many miscarriages. No gonorrhea	Positive		Ulcerating gumma on posterior wall	None	No tubercle bacilli. No gonococci
123	4th case	1928 F 27	Many miscarriages	Negative		Pseudo-membrane and ulcerative cystitis. No improvement with local treatment. 2nd and 3rd cystoscopic examination 1 yr. later showed papules	1 mo. after antiluetic treatment cure was obtained with control cystoscopy	
124	5th case	1928 M 58	Bilateral orchitis 2 yrs.	Negative		Fistulous orifice ½ cm. near right ureter with pus escaping	Under antiluetic treatment his physician reported clear urine	No tubercle bacilli. No gonococci
125	6th case	1928 F 36	Lues 10 yrs. Many miscarriages in recent years	Negative		Brownish red areas surmounted by yellowish papules of lentil size	Exclusive antiluetic treatment produced disappearance of all lesions	
126	7th case	1928 M 31	Cystitis since gonorrhea 7 yrs. ago. Local treatment failed	Positive		Ulcer with pseudo-membranous cystitis and yellowish papules on trigone	6 mos. after antiluetic treatment no symptoms and control—normal bladder	No tubercle bacilli. No gonococci
127	8th case	1928 F 35	Treated 20 yrs. ago for lues. 3 miscarriages since. Dry papules on leg	Positive		"Aspect de mure"	After 4 neoarsphenamine papules on leg disappeared and no symptoms. 2½ mos. later control—normal	No tubercle bacilli. No gonococci
128	9th case	1928 M 39	Rebellious gonorrhea 6 yrs.	Negative		Ulceration on trigone	After 1 injection—improvement. After 4 injections no symptoms and control—normal bladder	No tubercle bacilli. No gonococci
129	10th case	1928 M 61	Lues 20 yrs. ago. Denied gonorrhea or tuberculosis. Neurologic examination did not exclude lues	Negative 3 yrs. positive		Hypertrophy left lobe of prostate. Small miliary elevations over mucous membrane	After 6 bismuth all symptoms disappeared. Patient refused control	
130	11th case	1928 M 43	Gonorrhea 18 yrs. ago with stricture 12 yrs. Treated for lues and cystitis	Positive		Bullous edema of sphincter with small yellowish and red elevations about left ureter	After 3 bismuth all symptoms disappeared and control—normal bladder	No tubercle bacilli. No gonococci

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
131	Isnardi 1st case	1928 F 36	1 miscarriage. Husband suffered angina and treated for aortitis	Positive	Hematuria, frequency, dysuria, 7 mos.	Small capacity. Cystitis with red elevation near right ureter	2 mos. after neoarsphenamine symptoms disappeared and control—normal bladder. 6 mos. later no symptoms	
132	2d case	1929 M 29	Luetic roseola and general adenopathy-epitrochlear	Positive	Hematuria, frequency, dysuria, 1 mo.	Disseminated papules with macules on inflamed bladder base	After antiluetic treatment roseola faded and symptoms subsided. 1st control—macules disappeared. After 10 bismuth and 3 neoarsphenamine control—normal bladder	
133	Bisquett and Coutts	1928 F	Small vesicovaginal fistula	Positive		Lentil size lesions surrounded by red halo—"forme perlee" Fistula seen	After antiluetic treatment lesions disappeared and fistula closed	
134	Mertz and Miller	1929 F 34	Vesicovaginal fistula. X-ray chest suggestive of inactive tuberculosis. Spinal fluid, negative	Positive	Hematuria, frequency, dysuria, 6 mos.		After 3 mos. of non-specific treatment with no improvement, antiluetic treatment with mixed treatment was begun followed by neoarsphenamine. After 2 mos. marked improvement in fistulous tract and free from pain. Following tooth abscess—pneumonia—death.	Biopsy of fistula showed typical tubercles with characteristic giant-cells and tuberculous granulation
135	Orofino 1st case	1930 F 35	2 miscarriages	Positive	Frequency, dysuria	Whitish exudate over trigone with hyperemic areas	No result after 2 mos. irrigations. After 6 neoarsphenamine and silver nitrate irrigations symptoms disappeared and urine cleared. No control	
136	2d case	1930 F 29	No history of lues	Positive		2 ulcers on trigone and 1 ulcer near left ureter	After 6 daily mercury oxycyanide and irrigations symptoms disappeared and 20 days later control—normal	
137	3d case	1930 M 34		±		Bladder uniformly congested with bullous edema. No ulcers	After 3 neoarsphenamine — improved. After 30 injections control—slight congestion of trigone	
138	4th case	1930 M 28	Old gonorrhea	Negative		2 large ulcers behind trigone	1 mo. after mercury oxycyanide control—complete cure	
139	Raurich 1st case	1930 F 40	1 abortion. Luetic skin scars, deep ulceration of external genitalia, with ulcer at urethral meatus	Positive	Hematuria, frequency, dysuria, 5 mos.	After 12 days of antiluetic treatment cystoscopy possible edematous hyperemic areas with multiple superficial and deep ulcers on trigone	Control on 16th, 20th and 25th days after mercury oxycyanide showed regression of lesions. Frequency, dysuria disappeared on 15th day and hematuria on 30th day	No tubercle bacilli or gonococci. No other bacteria

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
140	2nd case	1930 F 37	Husband had chancre at 21 yrs. of age. Treated irregularly. No pregnancy in 15 yrs.	Positive	Hematuria, frequency, dysuria, 15 days	None	After 10 days irrigations and mercury oxycyanide for 12 days—symptom-free	
141	3d case	1930 F 18	Lesion on genitalia. Ulceration at meatus and superficial ulcer of labia. Macular skin eruption		Frequency, dysuria, 1½ mos.	Superficial ulceration on trigone	After 3 neoarsphenamine skin and labial lesions disappeared. 21 days after 5 neoarsphenamine all lesions healed and control—normal bladder	
142	4th case	1930 M 43	Chancre 20 yrs. ago with irregular treatment	Positive	Hematuria, frequency, dysuria, 8 mos.	Gummatous ulcer on lateral wall	Cured rapidly in 18 days on antiluetic treatment. No control	No bacteria
143	5th case routine observation	1930 F 38	Chancre 45 days. Strong roseola No treatment		Frequency, dysuria, 4 days	6 papules on trigone. 36 hours after 1st arsphenamine color increased. Herxheimer	On 20th day of treatment, control—normal bladder	
144	6th case routine observation	1930 F 31	Chancre 6 mos. Papules on abdomen and vulva		None	Papules with hyperemic halo	At the end of series of arsphenamine control—normal bladder	
145	7th case routine observation	1930 F 35	Chancre 4 mos. Papules on abdomen		Frequency, dysuria	Ulcer	After 1 mo. antiluetic treatment control—no ulcer	
146	8th case routine observation	1930 M 26	Recent scars from chancre—10 mos. Roseola—4 days		Frequency, dysuria	3 papules near neck	Symptoms disappeared after antiluetic treatment. No control	
147	Colodero and DiLella 1st case	1930 M 44	No venereal history. Left vesicle enlarged and tender	Negative	Hematuria, frequency, dysuria, 1 mo.	Vegetating lesions and ulcers on trigone and lateral wall	After 6 neoarsphenamine—no symptoms and control—all lesions practically disappeared	
148	2d case	1930 M 52	Gonorrhea at 16 years. Chancre untreated. X-ray negative. Large prostate	Negative	Frequency, dysuria	Retention. Large prostate. Infiltrated mamillated area with cystitis	After 2 neoarsphenamine—no symptoms and control—normal bladder. After 6 neoarsphenamine and 10 mesurol-negative	
149	Chocholka 1st case	1931 F 45	3 abortions. Bacteriology-negative	Negative	Frequency, dysuria, 3 yrs.	Grayish-white membrane over trigone	Local treatment failed. 2 mos. after potassium iodide no symptoms and control—disappearance of most of leucoplacic membrane	
150	2d case	1931 F 46	3 abortions. Specific ulcer at urethral meatus. Urethral stricture			Ulcer, edema and scars about neck of bladder with circinate cicatrices at right ureter	No control	No gonococci or tubercle bacilli

TABULATION OF CASES—Continued

Case	Author	Year Sex Age	History of syphilis or concomitant lesions	Wassermann	Genito-urinary symptoms—duration	Cystoscopic or operative findings	Results of specific treatment and cystoscopic control	Incidental bacteriology, histopathology or other laboratory findings
151	3d case	1931 M 65	Treated for lues 40 years ago. Hypertrophy of prostate	Positive	Frequency, dysuria	Ulceration and cicatrices all over bladder	Antiluetic treatment difficult because of cardiac complications. No control	
152	4th case	1931 M 48	No luetic history. Ulcero-fistulous condition of perineum and right testicle 3 yrs.	Negative	Frequency, dysuria, Few wks.	Pseudo-membrane with ulcerations	After 2 bismogenol felt well and urine clear. After 20 bismogenol complete cure and control—normal bladder. 1 yr. later castration showed orchitis, no tubercle bacilli	No gonococci or tubercle bacilli
153	5th case	1931 F 58	Right kidney movable, large and tender. Receiving treatment for gumma of knee		Frequency, dysuria	Trabeculation and edema. Catheter specimens from both ureters—white blood cells and albumin		
154	6th case	1931 M 62	Lues 15 yrs. ago. No gonorrhea. Nephralgia		Hematuria, frequency, dysuria, Few wks.	Papillomata. Urine from right kidney, pus, no gonococci, no tubercle bacilli. Urine from left kidney sterile	Antiluetic treatment recommended. No control	
155	Ajamil	1931 M 31	No venereal history. Fever 1 mo. Spinal fluid luetic curve and negative Wassermann. Prostate nodular	Negative	Frequency dysuria, 3 wks.	Villous-papillomatous growth of trigone. Cystogram—contracted bladder with irregular edges	2 days after neoarsphenamine lesions disappeared, only slight congestion remaining. Later urine cleared, and prostate became normal	Bacillus coli and streptococci in culture
156	Valverde 1st case	1932 M 34	Chancre 2 yrs. ago with specific treatment. Wassermann negative. After antiluetic treatment positive	Positive	Frequency, dysuria, 1½ yrs.	Syphiloma of left wall and left ureter orifice	1 mo. after antiluetic treatment syphiloma disappeared. Only slight edema remained. 2 mos. after antiluetic treatment control—normal bladder	Hyperplasia of endothelial cells with infiltration with mononuclear cells of chronic inflammation, lymphocytes and plasma cells. Cystic cavity in center with degenerating cells. Part homogeneous showing no structure and evidence of necrosis
157	2d case	1932 M 53	Gonorrhea at 30 yrs. with slight morning gleet. 20 yrs. Hematuria for few days 1 yr. ago	Positive	Hematuria	Vegetating syphiloma	3 days after antiluetic treatment hematuria ceased and dysuria improved. After 16 arsenic and 30 bismuth control—normal bladder. 3 mos. after 1st cystoscopy	Chronic inflammation with hyperplasia of epithelium 1 section shows hyperplasia of epithelium with tendency to anaplasia. In the chorion there is an infiltration with the cells of chronic inflammation
158	Levy and Tripoli	1933 F 20	2 injections of arsphenamine prior to operation for tubo-ovarian cyst causing abdominal pain, but no urinary symptoms	Positive	None	Operation revealed flat tumor (5 cm. x 1) overlying bladder. In freeing mass, the bladder was accidentally opened. Mass was adherent to left wall of uterus and contained necrotic material extending to iliac veins. Adjacent bladder wall—hard and friable. Bladder closed and drained urethrally. Suprapubic fistula developed	Cystoscopy after operation revealed the fistulous tract. In spite of antiluetic treatment, the patient died and necropsy revealed peritonitis and numerous whitish plaques diffusely distributed over bladder with tumor mass in right upper cornu of bladder showing central necrosis	Specimens at necropsy showed endarteritis with thrombosis and perivascular lymphocytic infiltration, occasional multinucleated giant cells and small areas of necrosis

18. Pugh, W. S. A. Med. J. & Rec., 1927, 126: 533–535.
19. Raurich, J. M. L. Rev. med. de Barcelona, 1930, 13: 391.
20. Saelhof, C. C. J. Urol., 1925, 13: 461.
21. Stokes, J. H. Modern Clinical Syphilology. Philadelphia: W. B. Saunders Co., 1928.
22. Valverde, B. Folha med., 1932, 13: 157–160.
23. Young. Practice of Urology, p. 337. By Young, 1926.

For Table

1. Ajamil, J. F. J. Urol., 1931, 25:53.
2. Arando. Abstracted by Chocholka (5, p. 132).
3. Asch, P. Ztschr. f. Urol., 1911, 5:504.
4. Avramovici. J. d'urol., 1926, 22:26.
5. Baker. Surg., Gynec. & Obst., 1917, 24: 187.
6. Barabas, E. Wien. klin. Wchnschr., 1925, 38: 123.
7. Beuc. Abstracted by Chocholka. Ztschr. f. Urol., 1926, 21: 132.
8. Bisquett and Coutts. Rev. méd. Lat.-Am., 1928, 13: 1145.
9. Blanc and Negro. J. d'urol., 1925, 19: 513.
10. Boeckel. Abstracted by Gaucher. Encycl. franç. d'urol., 4: 614.
11. Chocholka, E. F. J. d'urol., 1921, 12: 353.
12. Ibid. 1928, 25: 518.
13. Ibid. 1931, 31: 575.
14. Cirillo. Abstracted by Chocholka. Ztschr. f Urol., 1926, 21: 132.
15. Cole, F. H. Urol. & Cutan. Rev., 1918, 22: 480.
16. Coll. Abstracted by Chocholka. Ztschr. f. Urol., 1926, 21: 132.
17. Colodero and DiLella. Semana méd., 1930, 1: 1380.
18. Cosacesco. J. d'urol., 1921, 12: 345.
19. Ibid. 1922, 13: 365.
20. Danforth and Corbus. Surg., Gynec. & Obst., 1920, 31: 219.
21. DeGouvea, J. J. d'urol., 1924, 18: 388.
22. Denslow, F. M. J. Am. M. Ass., 1918, 70: 154.
23. Doureoux, L. Thesis de doct., Paris, 1912, p. 419.
24. Engelman, Von. Abstracted by Gaucher. Encycl. franç. d'urol., 4: 614.
25. Farago, S. Ztschr. f. Urol., 1922, 10:144.
26. Fowler, H. A. J. Am. M. Ass., 1917, 69: 1399.
27. Gautier, E. L. Bull. Soc. franç. d'urol., 1927, 6: 291.
28. Gayet and Favre. J. d'urol., 1914, 6: 35.
29. Ghiso and Puente. Semana méd., 1922, 1: 426.
30. Girard. Abstracted by Chocholka. Ztschr. f. Urol., 1926, 21: 132.
31. Gouvea, J. Tribuna med., Rio de Jan., 1916, 22: 173.
32. Graff, K. Beitrag zur Kenntniss der Blasensyphilis Dissertation, Freiburg, 1906.
33. Habenern. Abstracted by J. E. Windell. Urol. & Cutan. Rev., 1924, 28: 205.
34. Hesse. Dermat. Ztschr., 1918, vol. 25: Part 3.
35. Isnardi. Semana méd., 1928, 2: 297.
36. Ibid. 1929, 1:1040.
37 Kolischer and Eisenstadt. Surg. Clin. Chicago, 1919, p. 137.
38. Krotoszyner. Abstracted by J. E. Windell. Urol: & Cutan. Rev., 1924, 28: 205.
39. Le Fur. Ann. d. mal. d. org. génito-urin., 1902, 20: 1519.
40. Levy and Tripoli. Am. J. Obst. & Gynec., 1933, 25: 743.
41. Lucri, F. Jior. ital. di dermat. e sifil., 1925, 66: 1255.
42. Luttichau. Abstracted by F. Moses. Med. Klin., 1925, 21: 501.
43. MacGowan, G. J. Cutan. & Genito-urin. Dis., 1901, 19: 326.
44. Margoulies. Ann. d. mal. org. génito-urin., 1902, 20: 384.
45. Matzenauer. Arch. f. Dermat. u. Syph., 1900, p. 112.
46. Mertz and Miller. Indianapolis M. J., 1929, 32: 265.
47. Michailoff, N. A. Ztschr. f. Urol., 1912, 6: 215.
48. Molina, L. F. Rev. med. Cubana, 1927, 38:4.
49. Mucharinsky, M. A. Ztschr. f. Urol., 1912, 6: 376.
50. Nilson, G. Hygiea, Stockholm, 1916, 78: 540.
51. Nitkin, B. Zentralbl. f. Chir., 1928, 55: 660.
52. Orofino, A. J. d'urol., 1930, 29: 25.
53. Palma, A. A. Folha med., 1927, 8:100.
54. Papin. J. d'urol., 1927, Dec.
55. Pasteau. Abstracted by Chocholka. Ztschr. f. Urol., 1926, 21: 132.
56. Pedersen, J. Med. Rec., 1916, 89: 235.
57. Pereschiwkin, N. Ztschr. f. Urol., 1911, 5: 732.
58. Perucci. Abstracted by Chocholka. Ztschr. f. Urol., 1926, 21: 132.
59. Peterson, A. J. Urol., 1924, 12: 59.
60. Picker, R. Ztschr. f. Urol., 1913, 6: 192.
61. Idem. Ztschr. f. Urol. Chir., 1922, 11: 43.
62. Picot, G. J. d'urol. méd. et chir., 1912, 2: 693.
63. Posados. Abstracted by Gaucher. Encycl. franç. d'urol., 4: 614.
64. Pugh, W. S. M. J. & Rec., Nov. 2, 1927, 126: 533.
65. Raurich, J. M. L., Rev. med. de Barcelona, May, 1930, 13: 391.
66. Ries, K. Abstracted by R. Picker. Ztschr. f. Urol., 1922, 11: 43.
67. Ries, K. Monatschr. f. Harnkr. u. sex. Hyg., 1928, 1: 362.
68. Riley, A. Boston M. & S. J., 1926, 194: 874.
69. Ringleb. Abstracted by R. Picker. (61).
70. Rothschild, A. Ztschr. f. Urol., 1926, 21: 232.
71. Saelhof, C. C. J. Urol., 1925, 13: 461.
72. Schapira, S. W. Am. J. Urol., 1915, 11: 283.
73. Stotoerts. Abstracted by Chocholka. Ztschr., f. Urol., 1926, 21: 132.
74. Thompson, L. Am. J. Syph., 1920, 4: 50.
75. Turner, B. W. South. M. J., 1927, 20: 289.
76. Uras. Abstracted by Chocholka (5, p. 132).
77. Valverde, B. J. d'urol., 1932, 33: 142.
78. Wallace, W. J. Oklahoma M. Ass., 1918, 11: 186.
79. Watterson. Abstracted by J. E. Widell. Urol. & Cutan. Rev., 1924, 28: 205.

RUPTURE OF THE GRAAFIAN FOLLICLE AND CORPUS LUTEUM

W. FENN HOYT, M.D., AND JOE VINCENT MEIGS, M.D., F.A.C.S., BOSTON, MASSACHUSETTS
From the Surgical Services of the Massachusetts General Hospital

RUPTURE of the graafian follicle or corpus luteum of the ovary, whether physiological or pathological, may cause symptoms of severe or mild abdominal pain, may be serious enough to require immediate operation or may be so inconsequential that observation and rest in bed is the only treatment necessary. Certainly in many cases of "appendicitis" in young women operations have been done with a mistaken diagnosis. A more thorough knowledge of the symptoms and physical findings of this condition is important for all surgeons and gynecologists.

HISTORICAL

This entity is not a new one, but a large series of cases from one clinic is unusual. Ravdin found that Nélaton in 1851 was aware of the possibility of hemorrhage from a ruptured graafian follicle. H. W. Wilson in 1905 first reported finding a ruptured ovary at operation. In 1914, von Beust reported 36 cases which he had collected from the literature, and in 1917 Novak brought this number up to 40. In 1922, Moore added 14 cases. In 1924, Phaneuf analyzed the reported cases and found 42 cases of rupture of either the graafian follicle or the corpus luteum. In 1926, Brakeley and Farr added 14 more cases. R. K. Wilson, in 1928, supplied 7 additional cases. V. E. Johnson reviewed the literature in 1930 and found the total reported cases to be 77. Miller added 4 of his own in 1931; Boggon and Wrigley added 13; and Sackett added 26 cases of his own in 1932. Morton found the total number of cases reported through 1931 was 95. In 1933, we reported 25 cases from the Massachusetts General Hospital.

MATERIAL

In the years 1929 to 1934, inclusive, there have been in the Massachusetts General Hospital 58 patients who have had hemorrhage from rupture of the graafian follicle or corpus luteum that has caused symptoms severe enough to require operation. Such a series of cases brings attention to a problem of major proportions. The house officers and resident surgeons in the emergency ward have been looking for this condition in young women with abdominal pain. Consequently, an accurate diagnosis has been made before operation in 17 of the 58 cases; this is an unusual experience.

SYMPTOMS

Patients following rupture complain of sudden pain which is usually in the right lower quadrant. They may or may not have nausea and vomiting. In some instances the pain is extremely severe and the patient is greatly prostrated. This is most usual in those patients with large hemorrhages. Faintness occurs in the severe type. Pain at the top of the shoulder, which is noticed by some, is due to blood reaching the diaphragm, the pain being referred through the phrenic nerve.

ANALYSIS OF CASES

Of the 58 cases in this series, the ages of the patients range from 14 to 41. Thirty were between the ages of 15 and 20 years, and 14 between 21 and 25. Forty-eight were single and 10 were married.

Thirty-nine patients complained of a *sudden* sharp pain at the onset, 17 of a gradual onset, and 2 did not state the manner of onset of the pain. Forty-eight located the discomfort in the right lower quadrant. One had generalized abdominal pain finally localizing in the right lower quadrant. Another patient had left upper quadrant pain eventually localizing in the right side. In 1 case each, the pain was located in the lower abdomen, the right groin, and in the midline of the abdomen. One patient complained of having abdominal cramps.

Nausea was present in 22 cases, slight nausea in 13, and no nausea in 23 cases. Twenty-four patients had vomited while 34 did not.

Fainting at the onset occurred in those cases with severe hemorrhage as did pain at the top of the shoulder. Previous attacks had been experienced once by 8 patients, several attacks by 20 patients, and occasional discomfort by 1. Twenty-six patients had never had a similar attack while in 3 cases it was not stated. Only 1 patient had had a previous surgical operation which was for a ruptured ectopic pregnancy. The 57 others had never had a previous abdominal operation.

The previous menstrual cycle had been normal in 47 patients, irregular in 3, and was not mentioned in 6. One patient had a normal pregnancy 11 weeks previously and had not menstruated since the pregnancy. One had amenorrhea for 1 year and 1 month previous to her ruptured follicle. Considering the menstrual cycle as beginning

with the first day of menstruation, the rupture occurred on the following days of the cycle:

7th day	3
10th day	1
11th day	1
14th day	24
16th day	1
18th day	3
19th day	1
21st day	9
24th day	1
25th day	3
At onset	2
Not stated	9

PHYSICAL EXAMINATION

The physical signs, usually slight in the mild cases, were more severe if there was considerable hemorrhage.

Most of the patients were tender in the right lower quadrant but only a few had real spasm. The tenderness occasionally extended across the abdomen near the symphysis to Poupart's ligament and varied greatly with the amount of blood in the abdomen, those with a large amount of blood being exquisitely tender. Tenderness by pelvic or rectal examination was present in patients with blood in the pelvis. Motion of the cervix caused pain only when a considerable amount of fluid or blood was found.

The rectal temperature averaged 99.5 degrees but ran as high as 102 degrees. The pulse averaged 98 beats per minute, the highest being 130. Urinalysis was negative in all cases. The white blood count varied from 5,000 to 27,000, but was not done in 11 cases.

White blood count	Cases
5,000 to 10,000	22
10,000 to 12,000	9
13,000 to 14,000	8
15,000 to 17,000	2
19,000 to 20,000	3
21,000	1
24,000	2
27,000	1

The white blood count was normal or not higher than 10,000 to 12,000 in the mild cases. Patients with a large amount of blood in the abdomen had white counts which were more elevated.

DIAGNOSIS

The accurate diagnosis is difficult but can be made. In any differential diagnosis the possibility of such a lesion should always be considered. Not surprisingly, most of the mistakes were made in confusing the rupture with appendicitis. The pain and right lower quadrant tenderness are especially confusing. In the severe cases extrauterine pregnancy must be differentiated. To rule out such ectopic gestation is very difficult and there is no true differential point. Experience has taught us that even at operation such mistakes are not infrequent. Careful consideration must be given to the ovary to avoid calling a ruptured ovary an ectopic pregnancy.

The status of the menstrual period is of importance, for when the rupture occurs in the mid intermenstrual time it usually means a ruptured follicle and, when it occurs from the fourteenth day to the onset of the catamenia, it indicates bleeding from the corpus luteum. To make the diagnosis, a careful history concerning the onset of the pain, its suddenness and severity is essential. The presence of fainting and shoulder pain are very important. A careful menstrual history, especially noting the *beginning* of the last period, and the presence of previous similar attacks is also important. The pulse varies according to the amount of blood lost and the temperature with the time since the onset of the rupture.

The pre-operative diagnoses in this series were as follows:

Appendicitis	33
Ectopic pregnancy	2
Salpingitis	4
Tuberculous salpingitis	1
Ruptured graafian follicle	3
Ruptured corpus luteum	14
Undiagnosed	1

At operation ruptures of the ovary of the following types were found:

Ruptured graafian follicle	10
Ruptured corpus luteum	45
Ruptured corpus luteum cyst	1
Follicle or corpus luteum (ruptured) ?	2

Hemorrhage from the corpus luteum is much more frequent than from the graafian follicle. One patient also had an acute appendix, but here the diagnosis of appendicitis and ruptured corpus luteum were both accurately made.

TREATMENT

The authors believe that nearly every female patient who is operated upon for appendicitis should have a lower abdominal paramedian or midline incision. Through either incision the pelvis and ovaries can be explored under direct vision. Often the amount of blood or fluid from the rupture does not rise above the pelvic brim and, in several of the cases of rupture of the graafian follicles, thick clear coagulum has been found in the pelvis, which would be difficult to find through the ordinary incision for appendicitis.

When the abdomen is opened, either blood or bloody fluid may be easily detected. Sometimes it is necessary to explore the pelvis carefully in order to find a moderate amount of the coagulated material, and the ovary may show a recent opening without bleeding. If the rupture occurs so that a vein is torn, hemorrhage may ensue immediately. If the small hematoma, which normally forms in the ruptured follicle and represents the early stage of the corpus luteum, suddenly ruptures, hemorrhage occurs. This may take place any time from the rupture of the follicle to the onset of the next menstruation.

In our series the type of fluid present in the pelvis and abdomen was as follows:

Red blood	29
Blood stained fluid	15
Yellow fluid	4
Old blood	2
Not stated	8

Every effort should be made to conserve the ovary. In those who are actively bleeding the opening can be closed or the lining of the lesion can be shelled out and the defect closed with a fine atraumatic suture. A rubber covered gastric clamp, lightly placed on the ovarian blood supply, controls the hemorrhage while the ruptured area is being sutured.

The treatment of the ovary in this group was as follows:

	Cases
Nothing done	32
Mattress suture	7
Oophorectomy	11
Cyst removed	6
Both ovaries removed	1
Hysterectomy and oophorectomy	1

The right side was involved 39 times and the left 13 times and in 6 cases it was not stated. The appendix was removed in all cases except those with profuse hemorrhage and the pathological report of the removed appendix was negative in all but the acute case mentioned.

In retrospect many of these mild cases need not have been operated upon. The danger, in not operating, lies in the close resemblance the symptoms bear to those of acute appendicitis. In the cases of severe hemorrhage operation must be done.

IMPORTANCE OF DIFFERENTIAL DIAGNOSIS

According to most recent investigators, the time of rupture of the graafian follicle is at the mid point of the intermenstrual period. That is, the egg is released from the follicle on the twelfth to the fifteenth day following the onset of menstruation, or to put it another way from the twelfth to the nineteenth day before the oncoming period —(Ogino, Knaus, Shaw, Miller). It is at this time that pain may occur and some women, on careful history taking, will recall instances of such discomfort. Usually there is no pain; enough discomfort may be present, however, to decide the patient to visit a surgeon. Bleeding may conceivably occur from small veins about the follicle if the rupture is at all abnormal. At this time clear white to yellow coagulated material will be found in the pelvis, and if bleeding has occurred, a moderate amount of blood. After the follicle has ruptured, a blood clot forms in the ovary and the corpus luteum is in the process of forming. From such a body bleeding may easily occur and may be severe if the clot is loosened or mild if the bleeding comes from a small ruptured vein or its surface. The differential diagnosis between follicle and corpus luteum is not difficult and the operative findings usually decide which is responsible. Discomfort in any woman from the supposed time of ovulation to the oncoming menses may be due to rupture or bleeding.

The cause of the rupture is not clear but trauma has often been mentioned as a cause. We have not been able definitely to trace the cause to trauma in any of our cases. Cases have been reported by Christopher, Greeley, and others and most surgeons have been conscious of rupturing a small physiological cyst at one time or another. Trauma is conceivable as an etiological factor but a slightly abnormal ovulation or abnormal blood clot formation seems easier to consider the important factor.

It is necessary to realize that such happenings are possible, and it behooves us all to be on guard against a lesion suggesting appendicitis that may not need operation at all or that may need urgent surgery because of hemorrhage.

SUMMARY

1. Fifty-eight cases of rupture of the graafian follicle or the corpus luteum simulating other acute abdominal disease are reported.

2. Trauma has not been found to be an etiological factor in any case in this series.

3. The relation of the onset of symptoms to the day of the onset of menstruation is an important diagnostic point.

4. The sudden onset of pain, low temperature, slightly elevated pulse, and low white blood count, all out of proportion to the pain, are suggestive of this lesion in the mild cases.

5. Patients with severe hemorrhage following rupture show signs of a more diffuse tenderness,

are sometimes faint, and have referred phrenic nerve shoulder pain.

6. A lower abdominal paramedian or midline incision is advised, so that the ovaries may be explored under direct vision.

7. The ovary should be conserved if possible. The lining of the lesion may be shelled out and the ovary reconstructed with a fine atraumatic suture.

8. This normal or pathological physiology of the ovary should be considered in the differential diagnosis of acute abdominal pain.

BIBLIOGRAPHY

1. Beust, A. T., von. Lebensbedrochliche intraabdominelle Blutungen aus geplatzten Follicular-und Luteinrupten des Ovariums. Zurich, 1914.
2. Block, F. B. Am. J. Obst. & Gynec., 1930, 19: 102.
3. Boggon, R. H., and Wrigley, A. J. Lancet, 1931, 2: 1068.
4. Brakeley, E., and Farr, C. E. Am. J. M. Sc., 1926, 172: 580.
5. Christopher, F. J. Am. M. Ass., 1929, 93: 456.
6. Greeley, P. W. Illinois M. J., 1932, 61: 44.
7. Greenhill, J. P. Am. J. Obst. & Gynec., 1931, 22: 141.
8. Johnson, V. E. Am. J. Surg., 1930, 9: 538.
9. Meigs, J. V., and Hoyt, W. F. Am. J. Obst. & Gynec., 1933, 25: 532.
10. Miller, H. P. J. Am. M. Ass., 1931, 96: 1569.
11. Moore, E. C. Ann. Surg., 1922, 75: 492.
12. Morton, P. C. New York State J. Med., 1932, 32: 196.
13. Novak, E. J. Am. M. Ass., 1917, 68: 1160; Bull. Johns Hopkins Hosp., 1917, 28: 349.
14. Phaneuf, E. J. Am. M. Ass., 1924, 83: 658.
15. Ravdin, I. S. Surg. Clin. N. America, 1923, 3: 275.
16. Sackett, N. B. Am. J. Obst. & Gynec., 1932, 23: 849.
17. Shaw, W. J. Physiol. (London), 1925, 60: 193.
18. Wilson, H. W. Lancet, 1905, 1: 1196.
19. Wilson, R. K. Lancet, 1928, 1: 1221.

EDITORIALS

SURGERY, GYNECOLOGY AND OBSTETRICS

FRANKLIN H. MARTIN, M.D.
Founder and Managing Editor
1905–1935

ALLEN B. KANAVEL, M.D. ..... Editor
LOYAL DAVIS, M.D. ..... Associate Editor

DONALD C. BALFOUR, M.D. .... Associate, Editorial Staff

JANUARY, 1936

ACID ULCER

THE extensive literature and numerous current papers on all phases of gastric and duodenal ulcer testify both to the importance of the problem and to the prevailing uncertainty with respect to etiology and treatment. Indeed many writers go so far as to say that the cause of ulcer is entirely unknown, a stand which is hardly justified in view of the many facts which have been uncovered in various laboratories in the past few years. As a direct result of planned experimental procedures the disease has been caused to develop in the lower animal and to duplicate in almost every particular the lesion encountered in man. The gross and histological appearance of the experimental ulcer exactly resembles the clinical lesion, and it has been observed to perforate, to cause profuse hemorrhage, and to heal under a type of medical management which resembles that found effective in man. In addition the alterations in the physiology of the alimentary tract under which experimental ulcers may be expected to develop and become chronic are well understood and the factors involved may be fairly accurately appraised. It does not lessen the significance of this experimental work to concede that much of the knowledge is not new and that the evidence obtained from the lower animal in large part only substantiates older views that have arisen as a result of clinical experience and reflection.

The work of Exalto and of Mann and his associates provided for the first time a method for the regular production of ulcers in the intestines of dogs, without the use of external corrosive agents. Their finding that the diversion of bile and pancreatic juice to the exterior or into the lower ileum would lead to the development of perforating ulcers in that part of the small intestine which first receives the gastric content has been amply confirmed. There seems no reason to question the view that it is the neutralizing effect of the alkaline pancreatic juice which normally protects the duodenal mucosa from the acid gastric content. It is probable that the clinical application of this finding is not direct since it does not seem likely that bile and pancreatic juice often fail to reach the duodenum. A few such cases have, however, been observed. The chief significance of the work lies in the unequivocal support that it affords to the old theory that the corrosive action of the gastric juice, under certain circumstances, may produce and maintain a chronic ulcer.

The observations of the writer and his associates that all living tissues will succumb to the digestant action of the gastric juice, where conditions are such that they are exposed to the pure undiluted secretion, pro-

vides further support to the theory of the "peptic" genesis of ulcer. Whereas it was found that organs such as the spleen and kidney, when implanted into the wall of the normal stomach and consequently exposed to the usual gastric content remained little affected, they were promptly digested away when they were implanted into the wall of an isolated stomach pouch and exposed to the action of pure undiluted gastric juice. In a somewhat similar type of experiment it was demonstrated that the pure fundus secretion can digest away the normal mucosa of the alimentary tract including that of the stomach itself, the resulting defect displaying all the gross and histological features of chronic progressive ulcer in man. Under normal conditions the gastric juice is diluted and partly neutralized by swallowed food and saliva, the secretion of mucus from the pyloric antrum, and to a certain extent by the regurgitation of bile and pancreatic juice. Since the fundus secretion appears to be elaborated at a constant acidity it is clearly this neutralization that protects the mucosa from ulceration. A failure in this neutralizing mechanism would lead to the development of a progressive ulcer in the stomach or duodenum even though the mucosa was previously normal. This fact is of considerable significance since it makes it unnecessary to postulate a local loss of resistance of the mucosa to account for the lesion. The careful histological examination of a large number of resected stomachs in Konjetzny's material failed to reveal evidence of local vascular injury, embolism, or thrombosis, as called for in the theory of Virchow and Hauser. It is not to be supposed, however, that the resistance of the mucosa to digestion would always be uniform throughout or that a uniform exposure of the entire surface would always occur. Such variations should be of chief significance in determining the site of the resulting ulcer and its shape. The more general effect is manifested by the small erosions, hemorrhages, and cellular infiltrations in the neighboring more resistant or less exposed mucosa. According to this view the so called ulcer gastritis is of similar origin to the ulcer itself. It should be more amenable to medical treatment and perhaps for this reason is seen less frequently in those cases subjected to prolonged medical management before referred for surgical treatment.

A very important remaining problem is to outline those factors which lead to the accumulation in the stomach of a content that resembles pure gastric juice in acid and enzyme concentration. Pyloric stenosis with retention and excessive "continuous secretion" are two conditions which come readily to mind. Pyloric stenosis may raise the acidity of the gastric content by causing a long continued secretion of gastric juice and possibly also by preventing the backward regurgitation of duodenal secretions as indicated by the studies of Boldyreff and of Elman. The mechanism of the "continuous secretion" of gastric juice is little understood and the factors that alter its volume are unknown. There is evidence that this secretion is excessive in many ulcer patients, and is perhaps "nervous" rather than "humoral" in origin.

Of the two elements, pepsin and hydrochloric acid in gastric juice, it is the concentration of acid that determines the ability of the secretion to digest living tissue. When the legs of living frogs were exposed to the digestant action of gastric juice samples of varying acid and enzyme concentrations the extent of digestion was proportional to the concentration of acid and little if at all to the pepsin. Approximately 0.15 per cent free hydrochloric acid was the critical level below which the living tissue was not affected. When the acidity of the juice exceeded this level

the exposed living tissue was digested away although the pepsin concentration had been reduced to a tenth of its original value. It is doubtless significant that the free acidity of the normal gastric contents of man rarely exceeds 0.15 per cent (42 clinical units) and that higher values are commonly found in ulcer patients. The relatively greater importance of the acid in the genesis of ulcer is further suggested by certain observations made with pancreatic juice. The proteolytic enzyme of pancreatic juice, trypsin, is more active than pepsin but no "tryptic" ulcers of the duodenum in the region of the pancreatic ducts have been described. Furthermore the legs of living frogs exposed to pure activated pancreatic juice were not digested away as was the case with gastric juice. Accordingly if it seems wise to stress the importance of the chemical action of the gastric content in the etiology of ulcer of the stomach and duodenum the term "acid ulcer" is more accurate than "peptic ulcer" and serves to direct attention to the more important element in gastric juice.

LESTER R. DRAGSTEDT.

BONE TUMORS

GENERAL apathy of the medical profession regarding malignant bone tumors still prevails and is probably due to the exceedingly high mortality. This attitude in the past may also be ascribed to the confusion which existed, but the Registry of Bone Sarcoma of the American College of Surgeons has done much to clarify this subject. A classification has been given that can be comprehended by the average physician and has been the means of saving many limbs and probably a number of lives.

The diagnosis of bone tumors, and in fact many bone lesions, should be preceded by a systematic investigation of the clinical history, physical examination, biopsy (with gross and microscopic examination), and in many instances the response to irradiation by X-ray and radium. There is some difference of opinion regarding biopsy, and such an eminent authority as Ewing believes that an incision into a malignant bone tumor increases the danger of metastasis. However, a fairly large percentage of "five-year cures" give a history of repeated local operations. While it is quite true that an accurate diagnosis frequently can be made by experts without biopsy, the average well trained surgeon, without special experience is helpless. The safest procedure where the more malignant types are suspected is to prepare for a radical operation and make a frozen section while the patient is on the table; if there is evidence of malignancy, amputation or excision may be carried out. Only in case of doubt is it advisable to wait for the report from a permanent section. Frozen sections and sections made from needle or punch biopsies are not as dependable as permanent sections made from blocks of tissue removed surgically, but when confirming other evidence of malignancy, errors in diagnosis are exceedingly rare. One of the greatest difficulties which exists today is the paucity of pathologists who are experienced in bone pathology, and can render a reliable opinion. Differentiation between tumor bone and bone in the evolutionary process of repair, or reacting to the stimulus of inflammation, cannot always be made with ease. Distinction between solitary metastatic lesions and those of primary tumors, as endothelial myeloma, is exceedingly difficult. In very malignant tumors observed during the process of bone destruction, osteoclasts, the giant cell of normal bone repair, may be found in such great numbers that there may be a close resemblance to a benign giant cell tumor. The important practical point, whether the tumor is or is not malignant, can usually be

determined. Differentiation by roentgenogram between endothelial myeloma (Ewing's tumor) and osteogenic sarcoma can usually be made, though not pathognomonic, as each may simulate the characteristics of the other. Ewing's tumor responds rapidly to irradiation, while osteogenic sarcoma does not.

All bone tumors are potentially malignant as malignancy, though rare, has occurred even in tumors regarded as distinctly benign. Whether this originates from the inclusion of embryonic cells or from primary benign tumor cells is of no practical importance. For example: cases in which the diagnosis of giant cell tumor has been made by eminent authorities, have later proved to be definitely malignant. However, it is well known that almost 100 per cent of typical giant cell tumors can be cured by conservative measures. If the resemblance between rare malignant variants of giant cell tumors and typical giant cell tumors is so close that well trained men are not always able to make the distinction, from a practical point of view, the possibility of malignancy in apparently benign tumors must be considered, even though remote.

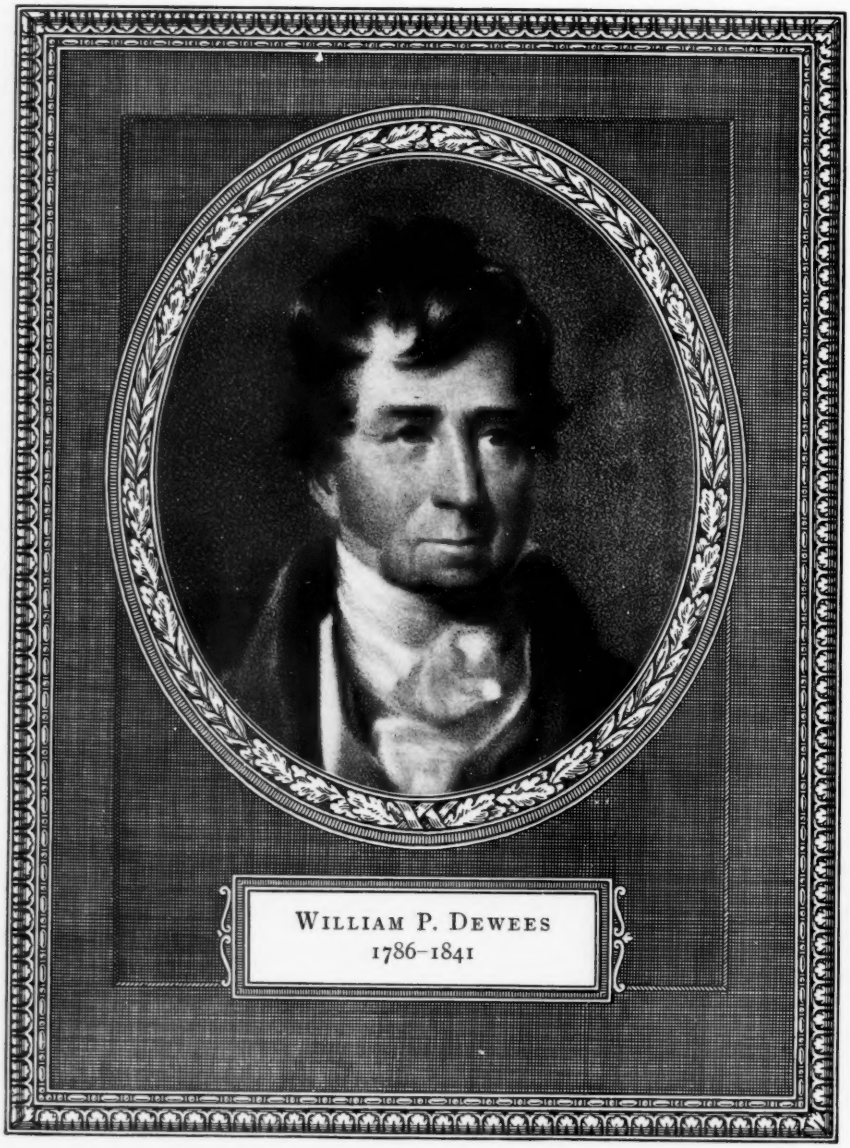
No arbitrary statement can be made as to time in relation to cure. Three of the 87 accepted "five year cures" of the Registry of Bone Sarcoma (B. S. R. No. 100, No. 970, and No. 1025) died of metastasis 11, 8, and 13 years, respectively, after treatment. However, if two years elapse without evidence of local recurrence or metastasis, the chances are good that the five year period will be reached. Many of the cases registered as "five year cures" were of low grade malignancy as demonstrated by the history, roentgenogram, and the histology, and even prior to registry, a fair percentage of these were cured by amputation or excision. However, there are possibly 25 per cent of those registered which were very malignant and are living and well after the elapse of 5, 10, or more years. The author has recently reported 14 cases which are living and well after the lapse of 3 to 16 years, 9 of which were malignancies of low degree, and 5 were very malignant. This is a vast improvement in results when compared to those of the past and is largely due to the study and advancement stimulated by the Registry. I presume the experience of other surgeons has been similar.

Secondary malignant changes have been observed in chronic bone lesions such as giant cell tumor, mentioned above, osteitis deformans (Paget's disease), osteochondroma, chondroma, low grade osteitis, etc. Some of these can be eradicated before malignant changes have occurred, but if eradication is impossible, by close observation one may detect malignancy in an exceedingly early stage. The same attention should be given to premalignant lesions of bone as is given to precancerous lesions, such as pigmented moles, scar tissue in the cervix, and lump in the breast.

Bone is a living tissue and must be so regarded, but the reaction to many pathological processes is exceedingly slow, and a long time may elapse, in some instances one or more years, before abnormal changes are demonstrable by the roentgenogram. In very malignant tumors the process is very rapid, and in all probability is demonstrable by the roentgenogram in its incipiency, but very few cases are ever observed before there has been extensive involvement. In our experience we have observed only two cases at a very early stage. One is living and well after three years, and one died as we were unable to make an early diagnosis. No one can give an expert opinion in such cases as so few are ever observed in the incipiency. The mortality still remains deplorably high, even if the diagnosis is made at a time which we now regard as early. But a carefully elicited history will

demonstrate that the diagnosis frequently could have been made weeks or months sooner.

The end-results in bone tumors, with our present knowledge of treatment, can be improved only by eradicating "pre-malignant" bone lesions, as stated above, and by a much earlier diagnosis and treatment of primary malignant tumors than is customary at the present time. It is conceivable that not only may the mortality be decreased, but also that less mutilating procedures may be successful. This can be accomplished only by co-operation of the profession and education of the public to the importance of carefully investigating symptoms of pain, with or without tumefaction, referable to bone, especially in children and young adults. WILLIS C. CAMPBELL.



WILLIAM P. DEWEES
1786–1841

MASTER SURGEONS OF AMERICA

WILLIAM POTTS DEWEES

THE subject of this sketch, William Potts Dewees, was born in Pottsgrove, Pennsylvania, in 1786. His paternal ancestors, the DeWees, were among the original Swedish settlers on the banks of the Delaware Bay and River. On the maternal side he was of English descent, his mother being a daughter of Thomas Potts, who was a member of the Society of Friends and for whose family Pottsgrove, or what is now Pottstown, was named.

Early in life he determined to study medicine. Although his early education was indeed scanty he had learned French and Latin. In order better to prepare him for his work his father placed him with a Dr. Phyle, a practicing apothecary, where he early obtained a knowledge of both pharmacy and chemistry. While still a young man his father died leaving little for his family.

After several years with Dr. Phyle, during which he showed considerable promise, he came to Philadelphia and apprenticed himself to Dr. William Smith. He not only assisted Dr. Smith but at the same time attended lectures in the University of Pennsylvania from which School he received, in 1789, at the age of 21, the degree of Bachelor of Medicine.

Following graduation he moved to Abington, a settlement some miles north of Philadelphia, where he became an active and ambitious practitioner. The thoroughness of his work was soon recognized and when in 1793 the yellow fever epidemic had seriously reduced the ranks of the medical profession of Philadelphia, Dewees was induced to move to that city to practice. This he did in December, 1793.

He entered upon the new field with considerable confidence not only because of the place he had made for himself but because his sponsor was Dr. Benjamin Rush. Rush was at this time an outstanding figure in American Medicine. Phillip Syng Physick and Thomas C. James, both of whom had only recently returned from study abroad were his associates and chief competitors. Physick, who became the Father of American Surgery, was without doubt an admirer of Dewees, for not long after his debut into Philadelphia he went to Dewees' defense when the latter was maligned by a jealous competitor.

The latter part of the nineteenth century found obstetrics in Philadelphia at a low ebb, for as Dr. Hodge has so aptly said, "at that period the science was

hardly known in America." Midwifery was largely in the hands of nurses and midwives. There was little instruction in it at the medical school. "The physicians who occasionally engaged in its practise had received no instruction, with the exception of a few, who had brought back a general knowledge of the subject from Europe. The existing prejudices against the employment of a male practitioner for obstetrics provided few opportunities and even fewer inducements for the physician to improve his knowledge in this field. Hence midwifery existed almost universally as an art; the aged and imbecile nurse was preferred to the physician."

The only training the student in the Philadelphia school could obtain was from Shippen who was already sorely pressed with his practice and his teaching of anatomy and surgery, and from Dr. Bond who with his already overburdened life had advertised on October 25, 1781, that in connection with his clinical lectures in medicine at the Pennsylvania Hospital he would teach obstetrics.

Dewees and Church early realized the opportunities in this field for supplying skillful and intelligent service. They began to perfect themselves and to communicate their knowledge and experience to others. Hodge's description of Dewees' early efforts is indeed interesting. "In a small office he collected a few pupils, and in a familiar manner indoctrinated them with the principles of our science, toiling year after year, in opposition to the prejudices not only of the community but even of the profession, who could not perceive that so much effort was necessary for facilitating the natural process of parturition."

In 1806 Dewees was given the degree of Doctor of Medicine by the University. His thesis was entitled "The Means of Moderating or Relieving Pain During Parturition." His work in this field was already bringing real recognition. "He has the high honor of first attempting a full course of Lectures on Obstetrics in America." It was, therefore, natural that he should be considered a candidate for the new chair of obstetrics but in spite of his qualifications and the warm support of Rush and Physick he failed to be elected, and Thomas Chalkley James was elected to the chair in 1810.

Under the apprehension of a pulmonary affection he was persuaded by friends to retire from the profession and to invest his capital in a farm near Phillipsburg, and here from 1812 to 1817 he lived as a farmer. He lost his capital and soon found that his talents lay in the practice of medicine rather than in farming so he returned to Philadelphia after 5 years to attempt to rebuild his practice.

In 1825, at the age of 57, he was elected adjunct professor of obstetrics and did much of the teaching of the department. He was then described as youthful because of his florid complexion and dark hair which was still "without the silvery gloss of age." He was exceedingly popular as a teacher although there was "no great display of eloquence or erudition in his lectures." He was clear and precise and his directions were given in great detail.

In 1834 he succeeded James as Professor, having done most of James' teaching for 10 years. The next fall he was so weakened in body and mind from apoplexy that his attempt to deliver the winter's course of lectures proved futile and in November, 1835, he resigned, retired from practice, and left for Havana to recuperate.

He practiced a little after this in Mobile, Alabama; for some 4 years, spent a short time in New Orleans, and returned to Philadelphia in 1840 "an altered man." He died on May 20, 1841.

Early in his work he had chosen to follow Baudelocque and the French School rather than the Osbornes and the English School. Nevertheless, this did not prevent the British from acclaiming his work, for in the July number of the British and Foreign Medical Review for 1839 was stated: "The Philadelphia School of Midwifery has for many years been looked upon with great respect by the obstetricians on this side of the Atlantic. The high name and professional standing of Dr. Dewees, his great experience, and above all his inestimable *Compendius System of Midwifery* and other valuable publications have mainly contributed to this result." Beside this system and his papers on various subjects he found time in his busy career to publish a *Treatise on the Diseases of Females*, one on *Diseases of Children*, and a *Practice of Medicine*. His system of midwifery went into the tenth edition. He was continually receiving certificates and diplomas from medical and other scientific bodies in the United States, the Canadas, and Europe. He was a member of the American Philosophical Society and a founder and first president of the Musical Fund Society.

Early in his career he married Martha Rogers, a daughter of Doctor Rogers of New England, who died a few years later. In 1802 he married Mary Lorain of Philadelphia. Although he was never known for elegance of manners he had warm affections and was deeply beloved by his patients. "He was during the long period of his active life a stranger to those higher sources of gratifications and happiness which arise from the communion of the soul of man with God, its Creator, but late in life he did turn to the Bible."

In his eloquent eulogy on Dewees delivered before the medical students of the University of Pennsylvania on November 5, 1842, Hugh L. Hodge, who was then professor of obstetrics in the University, said, "Nothing but a profound intellect could have raised him from the state of ignorance and poverty in which he was found by Dr. William Smith in the year 1786, to the first obstetric teacher in the United States. As already remarked, the character of his mind was that of strength rather than brilliancy or even originality; his judgment was unrivalled, and his memory most retentive." This then was the Father of American Obstetrics.

I. S. RAVDIN.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

A NARRATIVE of great interest is presented by Dr. Corlett in his volume[1] bringing together a large amount of scattered material on the ethnology, folklore, and social life of the Indians of North and South America. The book opens with a discussion of racial origins, followed by a chapter on Indian diseases and one on the "Medicine Man." Part 2 discusses in several chapters the special characteristics of the early inhabitants of North and South America. Part 3 is devoted to childbearing; Part 4 to foods and materia medica. The closing chapter constitutes a tribute to the first settlers of the Western world.

The volume contains so much of interest that one hesitates to point out minor deficiencies. Apparently the work of Dr. Edwin James has been overlooked. Then, too, one misses emphasis on the great Sioux nation, the most powerful of the plains' tribes and certainly the most interesting. In connection with the part on childbearing, one is reminded that George J. Engelmann's *Labor among Primitive Peoples* has never been adequately appreciated by American students of midwifery.

The bibliography is unusually rich and an excellent index is provided.

Both author and publisher are to be congratulated on the issuance of so attractive and valuable a volume. The format is all that could be desired.

IRVING S. CUTTER.

IT is delightful to read again Hertzler's essay on diseases of the thyroid gland.[2] The chief tenets of Dr. Hertzler's conception of thyroid disease stand out clearly. Goiter is a life long process leading to various clinical syndromata. This process can be interrupted by surgery and should be whether the patient is seven or seventy. The language of this presentation is often startling, occasionally slangy, but the meaning is usually the best common sense. "The important part of the study of a goiter in a child is the patient." "Cure the patient first and then attack the goiter problem, if any still remains."

A considerable portion of the text is devoted to the pathology of the thyroid removed at operation. A chapter on hospital management, pre-operative and postoperative by Dr. Chesky, is included.

In general, one can have no disagreement with the medical or surgical practice advised by this book. It is extremely hard to prove some things and Dr. Hertzler does not attempt to do so. No documentation accompanies the work. As he states in his preface, it is an expression of his own experiences and impressions but there is no statement of follow up. He stresses the value of prolonged direct follow up observation in arriving at a correct conclusion as to the adequacy of treatment. Yet throughout this book there is no presentation of clinical results and from one who has been following such patients for many years such an analysis would be very valuable.

PAUL STARR.

THERE are few students of medicine who are not acquainted with Cabot's *Physical Diagnosis*[3] which presents diagnostic methods and processes which are needed and used by competent practitioners, the first edition of which appeared in 1905. In this edition the same fundamental approach and high standard of scientific accuracy has been maintained, many revisions having been made. A chapter on electrocardiography has been added which seems somewhat superfluous in a book dealing with physical diagnosis. More detail has been given to the section on heart disease in which coronary disease is more adequately treated and pulmonary heart disease (Ayerza's disease) is briefly discussed. The section on tuberculosis has been enlarged by additions of new material on X-ray examinations in tuberculosis, latent tuberculosis, and tuberculosis in children. Cancer of the bronchi and lung appear in this edition for the first time. Many other additions, corrections, and omissions have been made to bring the subject matter on physical diagnosis up to date. The illustrations are graphic but a good number of these are old and made from old plates which detract from the up-to-dateness of this edition. Particular reference is made to that of page 186 (Fig. 153) in which we see a group of students in the dress of a quarter century ago. This book is as usable a text on the subject as is available.

H. B. CARROLL.

THE book by Emerson, entitled *The Nervous Patient*[4] is intended to familiarize the general practitioner with the disorders presented by the

[1] THE MEDICINE-MAN OF THE AMERICAN INDIAN AND HIS CULTURAL BACKGROUND. By William Thomas Corlett, M.D., L.R.C.P. (Lond.). Springfield and Baltimore: Charles C. Thomas, 1935.

[2] DISEASES OF THE THYROID GLAND. By Arthur E. Hertzler. With a chapter on Hospital Management of Goiter Patients by Victor E. Chesky, M.D. 3d ed., entirely rewritten. St. Louis: C. V. Mosby Co., 1935.

[3] PHYSICAL DIAGNOSIS. By Richard C. Cabot, M.D. 11th ed. Baltimore: William Wood & Co., 1934.

[4] THE NERVOUS PATIENT; A FRONTIER OF INTERNAL MEDICINE. By Charles Phillips Emerson, M.D. London, Philadelphia and Montreal: J. B. Lippincott & Co., 1935.

patient with nervous and mental disease. That such an attempt might serve a useful purpose is at once indicated by the fact that, although nervous and mental derangements are the most common of all disorders, the general practitioner is least acquainted with them, due to the neglect of neurology and psychiatry in the training of the physician. The general practitioner who feels that he is handicapped in his understanding of the patient with nervous and mental disease will find this book useful. Among the subjects covered are the emotions, migraine, the neuralgias, intracranial tumors, organic reaction types, dyskinesias, disorders of sleep, disorders of the sex life, the neuroses, the psychoses, epilepsy. Of necessity, many of the subjects are discussed briefly, sometimes the discussions are no more than extended definitions, but it contains much useful information and surprisingly few misstatements. The author's viewpoint throughout is very sane.

HARRY A. PASKIND.

THE attractive and beautifully illustrated volume[1] by von Lanz and Wachsmuth is a credit both to the industry and thoroughness of its authors, and to the art and skill of the printers and engravers who produced it.

Beginning with the upper extremity as a whole the authors consider in turn contour and form, superficial musculature, skeleton and skeletal development, arteries, veins, lymph vessels, nerves, nerve distribution, and the effects of nerve injury. Following a general survey each part of the upper extremity is taken in turn: shoulder, axilla, arm, elbow, forearm and hand, and the description of each region illustrated by plates, engravings, diagrams and line drawings—many of them in color—and portraying each part from many angles and aspects as well as in cross section.

This volume should be a welcome addition to the library of the surgeon who is interested in the surgery of the upper extremity, and of very real help to him as he prepares himself to attack the surgical problems in which it is involved.

SUMNER L. KOCH.

THE present volume, *Chirurgie de la tuberculose pulmonaire*,[2] is an excellent practical treatise on the surgery of pulmonary tuberculosis written by two of its most distinguished exponents. The authors have made no attempt to present a complete historical review and in the preface state definitely that the work is an exposition of the methods which they use personally and with which they have had an important experience. It has, therefore, the advantages and disadvantages of this limitation. While it loses something as a historical summary and a work of reference and bibliography, it gains much as a practical guide. The literature has been reviewed and referred to whenever it could throw light on the subject under discussion.

The first section considers the various theories which have been advanced to explain the retraction of the tuberculous lung and the principle of selective collapse. The extensive text and abundant illustrations describing the anatomy of the thorax and the technique of the operations are sufficient in themselves to make the volume valuable to any one interested in surgery of the chest, and the discussions of problems of surgical procedure are thorough and satisfactory.

The indications and results are not well dealt with. One cannot go to the book for information concerning the precise rôle of collapse therapy in the treatment of tuberculosis, and there are very few statistics on the results obtained from the different procedures. These are important aspects of the subject and while the authors undoubtedly considered that their concern was chiefly with matters of surgical procedure, one feels that chapters on the indications for collapse therapy in general and on its results would add greatly to the value of the work.

But this is to criticize the book for what it does not pretend to be and it is an excellent treatise on the surgery of pulmonary tuberculosis.

JEROME R. HEAD.

TO make the surgeons of our generation conscious of their indebtedness to Hugh Owen Thomas and to help them appreciate the background of Sir Robert Jones is a worth while undertaking; and we are much indebted to the author of this little volume[3] for making accessible in so interesting a form an account of Thomas' life and of his contributions to surgery. In its pages and illustrations there lives again the shy, slender, clear thinking, often irritable recluse who was both one of the earliest and one of the greatest of orthopedic surgeons. We see him with closely buttoned frock coat, with ever present cigarette, with cap tilted at a rakish angle over the left eye working in his surgery, correcting club feet, reducing dislocations, tapping and "damming" non-united fractures; and in the cramped quarters of Liverpool workmen and dock laborers treating compound fractures of the lower extremities; and in all his work achieving results on a par with those obtained today in a modern and well equipped hospital.

He did not, moreover, confine his work or his clear thinking to the problems of orthopedic surgery. He was interested in many fields of medicine and surgery; he was expert in the use of the lithotrite; he advocated rational methods of treatment of typhoid fever and of intestinal obstruction that are recognized as such today and that are in accord with modern therapeutics. He "had a coherent method

[1] PRAKTISCHE ANATOMIE; EIN LEHR- UND HILFSBUCH DER ANATOMISCHEN GRUNDLAGEN AERZTLICHEN HANDELNS. By Dr. T. von Lanz and Dr. W. Wachsmuth. Vol. 1, part 3—Arm. Berlin: Julius Springer, 1935.

[2] CHIRURGIE DE LA TUBERCULOSE PULMONAIRE; INDICATIONS, TECHNIQUES, RÉSULTATS. By A. Bernou and H. Fruchaud. Paris: C. Doin et Cie, 1935.

[3] HUGH OWEN THOMAS: HIS PRINCIPLES AND PRACTICE. By D. McCrae Aitken, M.A., M.B., Ch.B. (Ed.), F.R.C.S. (Ed. and Eng.) London: Oxford University Press, 1935.

of treatment based on the principle of physiological rest for any inflamed tissue," and this principle he applied in a logical manner to all the problems associated with inflammation, no matter in what part of the body.

The surgeon of today needs to know more of the great heritage of the past; and Aitken's volume will help him to realize more keenly the debt of all surgeons and, particularly, of orthopedic surgeons to Hugh Owen Thomas. SUMNER L. KOCH.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

DISEASES OF THE NOSE AND THROAT; FOR PRACTITIONERS AND STUDENTS. By Charles J. Imperatori, M.D., F.A.C.S., and Herman J. Burman, M.D. Philadelphia, London and Montreal: J. B. Lippincott Co., 1935.

THE STOMACH AND DUODENUM. By George B. Eusterman, M.D., F.A.C.P., and Donald C. Balfour, M.B., M.D.(Tor.), LL.D., F.A.C.S., F.R.A.C., and Members of the Staff. Philadelphia: W. B. Saunders Co., 1935.

DISEASES OF WOMEN. By Harry Sturgeon Crossen, M.D., F.A.C.S., and Robert James Crossen, M.D. 8th rev. ed. St. Louis: The C. V. Mosby Co., 1935.

GROWING SUPERIOR CHILDREN. By I. Newton Kugelmass, M.D., Ph.D., Sc.D. New York and London: D. Appleton-Century Co., 1935.

MECHANICS OF NORMAL AND PATHOLOGICAL LOCOMOTION IN MAN. By Arthur Steindler, M.D., F.A.C.S. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1935.

THE 1935 YEAR BOOK OF RADIOLOGY. Diagnosis. Edited by Charles A. Waters, M.D., Associate editor, Whitmer B. Firor, M.D. Therapeutics edited by Ira I. Kaplan, B.Sc., M.D. Chicago: The Year Book Publishers, Inc., 1935.

MÉDECINE ET CHIRURGIE PRATIQUES. Traitement de l'éclampsie; technique actuelle du traitement prophylactique. By B. Stroganoff. Paris: Masson et Cie, 1935.

TUMORS OF THE URINARY BLADDER. By Edwin Beer, M.D. Baltimore: William Wood & Co., 1935.

CLASSICAL CONTRIBUTIONS TO OBSTETRICS AND GYNECOLOGY. By Herbert Thoms, M.D. With a foreword by Howard A. Kelly. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1935.

JOHN WHITRIDGE WILLIAMS; ACADEMIC ASPECTS AND BIBLIOGRAPHY. By J. Morris Slemons. Baltimore: The Johns Hopkins Press, 1935.

SURGERY, QUEEN OF THE ARTS; AND OTHER PAPERS AND ADDRESSES. By William D. Haggard, M.D., F.A.C.S., D.C.L. Philadelphia: W. B. Saunders Co., 1935.

REGIONAL ANATOMY; ADAPTED TO DISSECTION. By J. C. Hayner, B.S., M.D. Baltimore: William Wood & Co., 1935.

PRESCRIPTION WRITING AND FORMULARY; THE ART OF PRESCRIBING. By Charles Solomon, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1935.

VEIT'S HANDBUCH DER GYNAEKOLOGIE. 3d rev. enl. ed. Edited by Dr. W. Stoeckel. Vol. 4, 2nd half—KLINIK DER GYNAEKOLOGISCHEN ROENTGENTHERAPIE. 2d part—DIE BEHANDLUNG DER BOESARTIGEN GESCHWUELSTE. By H. Wintz and F. Wittenbeck. Munich: J. F. Bergmann, 1935.

ANTENATAL AND POSTNATAL CARE. By Francis J. Browne, M.D.(Aberd.), D.Sc., F.R.C.S.(Edin.), F.C.O.G. London: J. & A. Churchill, Ltd., 1935.

LOCALIZED RAREFYING CONDITIONS OF BONE; AS EXEMPLIFIED BY LEGG-PERTHES' DISEASE, OSGOOD-SCHLATTER'S DISEASE, KUEMMELL'S DISEASE AND RELATED CONDITIONS. By E. S. J. King, M.D., D.Sc., M.S.(Melb.), F.R.C.S.(Eng.), F.R.A.C.S. Baltimore: William Wood & Co., 1935.

THE PATIENT AND THE WEATHER. By William F. Petersen, M.D. Vol. 1. Part 1. The Footprint of Asclepius. Ann Arbor, Mich.: Edwards Brothers, Inc., 1935.

LIPPINCOTT'S NURSING MANUALS. Principles of Ethics. By Dom Thomas Verner Moore, Ph.D., M.D. Philadelphia, Montreal, and London: J. B. Lippincott Co., 1935.

DEMONSTRATIONS OF PHYSICAL SIGNS IN CLINICAL SURGERY. By Hamilton Bailey, F.R.C.S.(Eng.). 5th rev. ed. Baltimore: William Wood & Co., 1935.

THE PARATHYROIDS IN HEALTH AND IN DISEASE. By David H. Shelling, B.Sc., M.D. St. Louis: The C. V. Mosby Co., 1935.

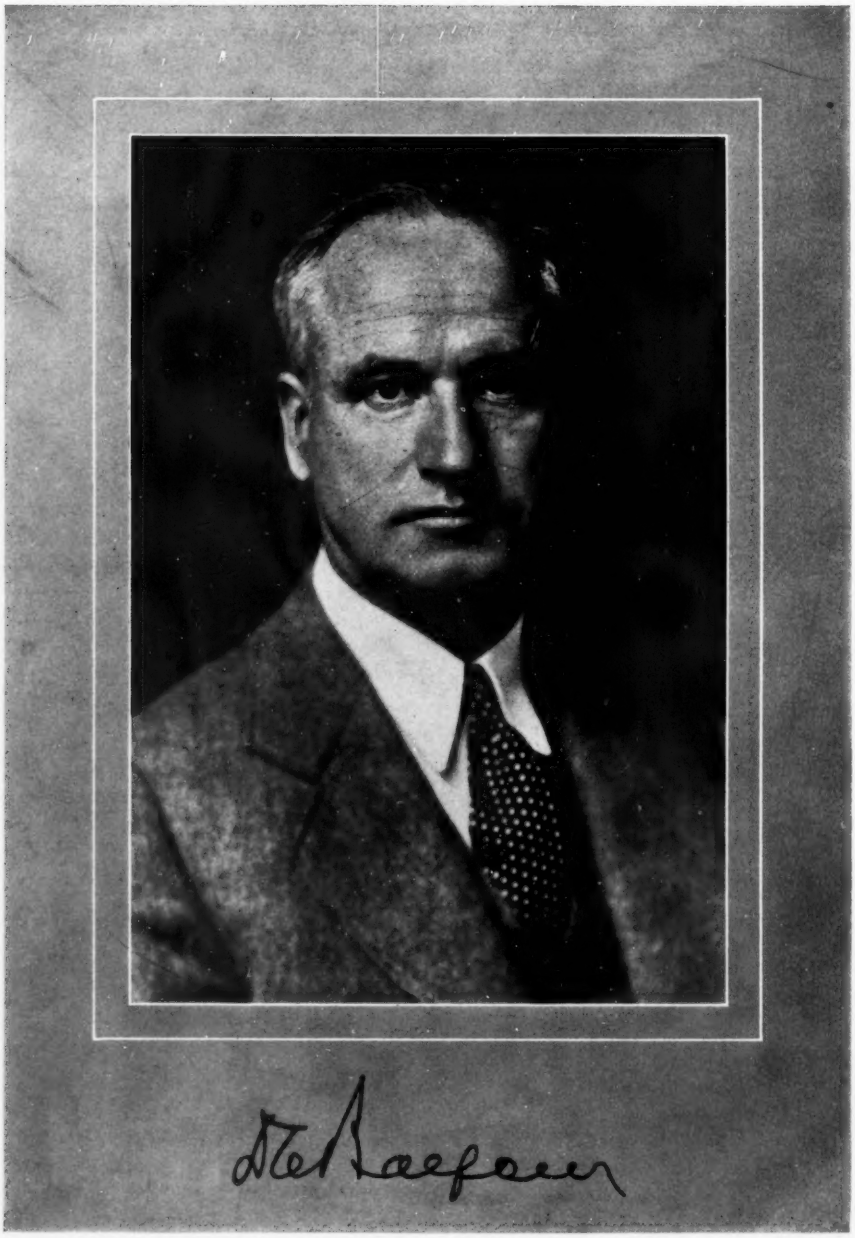
ATLAS OF PATHOLOGICAL ANATOMY; ISSUED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE OF THE BRITISH JOURNAL OF SURGERY. Compiled by E. K. Martin, M.S., F.R.C.S. Vol. 2. Baltimore: William Wood & Co., 1935.

THE RADIOLOGY OF BONES AND JOINTS. By James F. Brailsford, M.D.(B'ham), M.R.C.S.(Eng.). 2d ed. Baltimore: William Wood & Co., 1935.

THE ROCKEFELLER FOUNDATION. International Health Division. Annual Report 1934. New York.

THE CERVIX UTERI; WITH SPECIAL REFERENCE TO THE DEVELOPMENT OF CANCER. By R. Francis Matters, M.D., M.S., F.R.C.S.E., F.R.A.C.S., M.C.O.G., D.G.O. Adelaide: The Hassell Press, 1935.

A MARRIAGE MANUAL; A PRACTICAL GUIDE-BOOK TO SEX AND MARRIAGE. By Hannah M. Stone, M.D., and Abraham Stone, M.D. New York: Simon and Schuster, 1935.



PRESIDENT 1935-1936